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SPECIAL LISTING

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CURRENT CANCER RESEARCH

on

ENDOCRINE NEOPLASMS: DIAGNOSIS, TREATMENT, AND PATHOPHYSIOLOGY

MAY 1981

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 50 different cancer research areas are covered by a separate **SPECIAL LISTING**.

The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 50 different countries. Researchers are urged to prepare accurate summaries which will be rapidly processed for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS**.

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RESEARCH AREAS

	Abstract Number
I. PITUITARY TUMORS	1
A. DIAGNOSIS AND THERAPY	1
B. PATHOPHYSIOLOGY	15
II. THYROID AND PARATHYROID TUMORS	19
A. SCREENING	19
B. DIAGNOSIS	31
1. IMMUNODIAGNOSTIC METHODS	31
2. OTHER DIAGNOSTIC METHODS	37
C. PATHOPHYSIOLOGY	45
D. THERAPY	58
III. ADRENAL TUMORS	63
IV. PANCREATIC TUMORS	68
A. DIAGNOSIS	68
1. IMMUNODIAGNOSTIC METHODS	68
2. RADIODIAGNOSTIC METHODS	84
3. BIOCHEMICAL AND OTHER DIAGNOSTIC METHODS	92
B. PATHOPHYSIOLOGY	104
C. THERAPY	118
1. CHEMOTHERAPY	118
2. RADIOTHERAPY	131
3. COMBINED MODALITY AND OTHER THERAPEUTIC METHODS	137
V. OTHER STUDIES OF ENDOCRINE OR HORMONE-PRODUCING NON-ENDOCRINE TUMORS	147

Investigator Index

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CURRENT CANCER RESEARCH

I. PITUITARY TUMORS

A. DIAGNOSIS AND THERAPY

1. INFERIOR PETROSAL SINUS CATHETERIZATION IN DIAGNOSIS AND TREATMENT OF PITUITARY TUMORS

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Inferior petrosal sinus opacification by retrograde venography has been used at several centers as an alternate technique for opacification of orbital veins. In addition, the procedure delineates the anatomy of the cavernous and intrasellar venous sinuses and provides an opportunity for obtaining blood samples directly from the cavernous sinuses. We propose that it may offer definitive methods for the diagnosis of pituitary tumors and that sampling the effluent for hormones will provide evidence for the source of hypersecreted hormones when that source is in doubt. To establish whether this is the case, patients with disorders of the pituitary-adrenal axis who are undergoing continuous venous catheterization for other reasons will have sampling of the inferior petrosal sinus for hormone measurement, and, when indicated, opacification of the cavernous sinus.

2. HORMONES IN CEREBROSPINAL FLUID

Kendall, J. W., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Sam Jackson Park Rd., Portland, Oregon*, 97207, United States of America

A reevaluation of the significance of pituitary hormones in cerebrospinal fluid has followed the accumulation of a larger series of patients. Most pituitary hormones are present in CSF of normal patients in very low concentrations. Prolactin, for reasons not completely clear, is present in normal patients in relatively higher concentrations so that the ratio of plasma to CSF prolactin concentration is normally about 10:1. In patients with intrasellar pituitary tumors or with the empty-sella syndrome CSF values of all hormones measured (growth hormone, ACTH, TSH, LH, FSH), except prolactin, are at low concentrations similar to those in normals. Prolactin values maintain, however, the same ratio as in normals. In contrast, in patients with suprasellar tumors, CSF values of individual hormones may be very high, suggesting direct release from the tumor into adjacent CSF spaces. Prolactin also may rise inappropriately (plasma:CSF ratio, 10:1) so that prolactin determinations are of value in assessing suprasellar extension. Additionally, a fall in CSF hormone values after surgical treatment has been found in patients successfully treated for suprasellar tumors. A determination of CSF pituitary hormone values therefore is useful when: 1) Patients are unable or unwilling to have a pneumoencephalogram, and 2) in follow-up of prior treatment for suprasellar extension.

3. DIAGNOSIS OF PROLACTIN-SECRETING PITUITARY TUMORS AFTER L-DOPA

Fang, V. S., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

4. SAFER CANCER CHEMOTHERAPY - THE DESIGN OF MULTIPLE DRUG PROTOCOLS (ABBREV)

Hill, B. T., Price, L. A., Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The use of antitumor drugs has traditionally been reserved for patients who fail to respond or whose tumors have recurred after standard treatment with radiotherapy and surgery. This understandable reluctance to use chemotherapy, except as a last resort, derives from the mistaken belief that drug therapy is automatically associated with severe toxicity. We have shown that, provided certain precautions are observed, it is possible to administer intensive combination chemotherapy protocols, designed according to certain kinetic principles (see ICRF Scientific Report 1976 - report 59), with safety and without loss of therapeutic benefit. This approach, involving treatment over 24-36 hours rather than several days, has been used effectively against certain advanced malignancies. For example, head and neck cancers (ICRF Scientific Report 1978 - report 18), breast carcinomas (Goldie and Price, British Medical Journal, 1977, 2. 1064) and non-squamous cell lung cancers (Anderson et al. British Journal of Diseases of the Chest, 1977, 71, 179). Ongoing studies include the treatment of advanced endometrial carcinomas (ICRF Scientific Report 1978 - report 20) where 2/6 responses have been noted and pancreatic tumors (in collaboration with Dr. J. Angers, New York, USA) involving treatment with vincristine, mitomycin C, procarbazine, chlorambucil, 5-fluorouracil and pyrimethamine.

Recently we have designed trials based on these principles, for cervical cancer in collaboration with Johannesburg, and for prostatic cancer for the Multicentre U.K. trial. These protocols are all well tolerated by the patients and allow a good quality of life. This safe and effective method of administering combination chemotherapy can now be used to complement local therapy.

5. METABOLIC PATTERNS AND CHEMOTHERAPY OF NEOPLASIA

Weber, G., Ban, J., Aoki, T., Suttle, D. P., Indiana University, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Pharmacology, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

BACKGROUND: With present-day treatment, radiation and surgery are capable of curing approximately 50 percent of cancer patients; consequently, effective chemotherapy applicable to most or all cases of neoplastic diseases is urgently needed. Chemotherapy has already shown encouraging progress in the treatment of choriocarcinoma, Burkitt's lymphoma, certain other types of lymphomas and juvenile leukemias, Hodgkin's disease and certain endocrine tumors. However, in the great majority of solid tumors, adult onset leukemias, and especially brain tumors, chemotherapeutic efforts so far have failed to produce lasting results and there is a great deal to be achieved in the rational design of chemotherapy for cancer and allied diseases.

AIM OF THE RESEARCH PROGRAM: (1) The objective of this investigation is to elucidate strategic exploitable metabolic, enzymatic and isozymic differences between normal and neoplastic tissues of different growth rates and differentiation to provide a molecular basis for rationally planned selective enzyme pattern-directed experimental chemotherapy. (2) A thorough understanding of the main differences between normal and cancerous tissues at the molecular level should permit the evaluation of the regulatory mechanisms of gene expression which play crucial roles in the differentiation, replication and functioning of normal and neoplastic cells. It is expected that

elucidation of the enzymatic basis of the key metabolic and regulatory alterations in cancerous tissues and an understanding of the factors which govern the pattern of gene expression might permit the design of new drugs and approaches to control neoplastic diseases by chemotherapy. (3) The ultimate goal of this program is to identify key metabolic, enzymatic and isozymic targets for chemotherapy and to develop chemical compounds possessing a high degree of selective toxicity to cancer cells in order to achieve lasting chemotherapeutic results.

6. GENERAL CLINICAL RESEARCH CENTER

Grover, M. R., Porter, J. M., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon,* 97201, United States of America

The Clinical Research Center at the University of Oregon Health Sciences Center is currently conducting human research across a wide number of human disease states as well as numerous physiologic and pharmacologic observations on normal volunteers. Subjects under active investigation at the present time include: (1) solid tumor chemotherapy, (2) progesterone, prolactin and estrogen interaction and manifestations in metastatic breast carcinoma, (3) hyperlipidemia and cholesterol metabolism, (4) Raynaud's syndrome and other vasospastic diseases, (5) autoimmune diseases, (6) bronchial asthma, (7) effect of methadone on respiration, (8) investigations of new diuretic agents, (9) studies on growth hormone, (10) agammaglobulinemia, (11) hyperlipidemia of renal disease, (12) evaluation of floctafenine, (13) blood pressure control, (14) parathormone secretion in end-stage renal disease and parathyroid secretory function after parathyroidectomy, and (15) evaluation of hypersecreting pituitary tumors.

7. A RANDOMIZED STUDY FOR THE TREATMENT OF CHROMOPHOBE ADENOMAS OF THE PITUITARY GLAND WITH IRRADIATION

Strott, C., Kahn, C. R., Roth, J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Child Health & Human Development, Endocrinology & Reproduction Research Branch, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Since the natural history of chromophobe adenomas unassociated with visual impairment is uncertain, the approach to therapy in patients with this disorder is controversial. Complications often attributed to tumor growth may, in fact, be sequalae of the treatment administered, whether it be radiotherapy or surgery. The purpose of this project is twofold: 1) To observe the natural history of untreated chromophobe adenomas in patients who do not present initially with visual disturbances and 2) to compare their clinical course with that of patients treated by one commonly employed modality, i.e., radiation therapy. Thus, patients will be randomized into two groups: one group will receive no therapy and one group will be treated with conventional pituitary irradiation. In a sense each group is serving as a control for the other group. Over the study period specific clinical and laboratory abnormalities will be assessed in each group and compared in an attempt to help guide physicians in the treatment of this disorder.

8. IMMUNOCYTOCHEMISTRY OF HUMAN BRAIN TUMORS

Kirsch, W. M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1055 Clermont St., Denver, Colorado,* 80210, United States of America

We have screened over 150 human brain tumors for the presence or absence of SV40 T-antigen. Two tumors were highly suspicious for the presence of T-antigen: one a human ependymoblastoma, the other a choroid plexus papilloma. In addition, we have developed a radioimmunoassay for T protein, which is applicable to extracts of human tumors. In addition, our immunocytochemical studies have been extended to include the identification of various hormones and pituitary tumors. This includes growth hormone, ACTH, and prolactin. We have developed a frozen section method, which will be applicable to the study of human pituitary tumors removed at surgery. We have concluded that T-antigen is not a significant componen: of human tumors, particularly meningiomas, but that a frozen section technique may have application in surgical treatment of pituitary adenomas.

9. BROMOCYPTINE FOR PROLACTIN SECRETING PITUITARY ADENOMA (HUMAN)

Yen, S. S., University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California,* 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

10. THERAPY OF PROLACTIN AND SOMATOTROPIN SECRETING TUMOR WITH MEGAVOLTAGE RADIATION

Camargo, C. A., Stanford University, School of Medicine, Dept. of Endocrinology & Metabolism, *300 Pasteur Dr., Stanford, California,* 94305, United States of America

This is part of a broader project. A summary of this subproject is not available.

11. PITUITARY FUNCTION AFTER SURGICAL REMOVAL OF PITUITARY ADENOMA (HUMAN)

Givens, J. R., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Medicine, *62 S. Dunlap St., Memphis, Tennessee,* 38103, United States of America

This is part of a broader project. A summary of this subproject is not available.

12. EVALUATION OF PITUITARY ADENOMA IRRADIATION (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

13. TRANSPHENOIDAL ADENOMA REMOVAL FOR HYPERSECRETING PITUITARY TUMORS

Greer, M. A., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon,* 97201, United States of America

This is part of a broader project. A summary of this subproject is not available.

14. PRE- AND POST-OPERATIVE STUDY OF PATIENTS WITH PITUITARY TUMOR

Robinson, A. G., University of Pittsburgh, School of Medicine, Dept. of Medicine, *3550 Terrace St., Pittsburgh, Pennsylvania,* 15261, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. PATHOPHYSIOLOGY

15. PITUITARY ADENOMAS - STRUCTURE-FUNCTION RELATIONS

Ezrin, C., Kovacs, K., University of California, Los Angeles Campus, Cedars-Sinai Medical Center, *8720 Beverly Blvd., Los Angeles, California,* 90048, United States of America

We have developed a new classification of human pituitary adenomas, based on immunocytochemistry and electron microscopy. From further study of additional tumors we expect to establish the incidence, clinical and laboratory characteristics and response to treatment of these separate tumor types. This new functional classification should be of help to pathologists, endocrinologists, neurosurgeons and others dealing with human pituitary tumors. We have been asked to write a chapter describing our experience with this new classification for the Armed Forces Institute of Pathology's revised fascicle on pituitary tumors.

16. HYPOPHYSEAL ADENOMAS

Angeles, A., Ramirez Mendoza, P., Hospital General de Mexico, Anatomia Patologica, *Colonia de los Doctores, Dr. Balmis, 148 ZP 7, Mexico City 7, D.F., Mexico*

OBJECTIVE: To review and classify, in accordance with new histochemical techniques, the cases of surgical and autopsy specimens of hypophyseal adenoma recorded in the files at the Hospital General de Mexico, D.F. SSA.

METHODS: Using current histochemical techniques, paraffin blocks or organs fixed in formaldehyde obtained from all

cases diagnosed as hypophyseal adenoma will be treated and stained. The cases will be evaluated according to the classification proposed in 1977 by Kovacs. A review of the literature covering the last 10 years will also be prepared.

PROGRESS: We are completing the bibliographic review and review of files. The evaluation of our findings has not yet begun.

17. GLUCOREGULATION OF ANTERIOR PITUITARY HORMONE SECRETION

Hagen, T. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Endocrine-Metabolic Section, *5000 W. National Ave., Wood, Wisconsin,* 53193, United States of America

As was noted last year, the direction of this protocol has changed to continue to follow up important observations on peripherally circulating releasing factor-like materials, namely, CRF and PRF. Since the last annual report, we have published data suggesting that circulating PRF is increased in patients with prolactin secreting pituitary disorders and that the level of PRF correlates very significantly with the prolactin level in the same sample. Additional studies of PRF-like material presented to the Endocrine Society in June of 1978 suggest that the material elutes from Sephadex G-25 in a position close to LHRH and TRH, suggesting that the material is a small molecule. Studies are in progress to further isolate the material and subject it to pronase and other materials to identify its chemical nature. Additional studies indicate that PRF-like material is present in rat plasma as well as in human plasma and that an identical extraction of rat hypothalami also extracts a PRF. Studies in the rat indicate that serotonergic mediation of prolactin increases directly involves PRF, and that no apparent inhibition of the dopamine inhibitory pathway is involved. Further human physiologic studies suggest that PRF increases when prolactin is suppressed by dopamine infusion. The bioassay is not sensitive enough to detect a fall in PRF when prolactin levels are increased with chlorpromazine. Lastly, the CRF bioassay has been improved in terms of sensitivity to the point where 0.2 hypothalami significantly increase in vitro ACTH release above buffer using a dispersed cell system. We are currently assessing the sensitivity of this modified bioassay for human plasma extracts.

18. ENDOCRINOLOGY ASSESSMENT OF PITUITARY ADENOMA (HUMAN)

Thorner, M. O., University of Virginia, School of Medicine, Dept. of Medicine, *Box 246, Charlottesville, Virginia,* 22901, United States of America

This is part of a broader project. A summary of this subproject is not available.

II. THYROID AND PARATHYROID TUMORS

A. SCREENING

19. DIAGNOSING MEDULLARY CARCINOMA OF THE THYROID - RESULTS OF SCREENING IN SIX FAMILIES WITH SIPPLE'S SYNDROME

TeleniusBerg, M., Lunds Universitet, Dept. of Oncology, *Box 50, S23053 Alnarp, Sweden*

Sixty-four members of 6 families with Sipple's syndrome (hereditary medullary carcinoma of the thyroid (MCT) and pheochromocytoma) have been examined in a screening program that was started in 1969. By December 1978 35 of 64 (55%) had been shown to have MCT while only one third of those had pheochromocytomas. The best diagnostic method was the determinations of S-calcitonin before and after i.v. administration of pentagastrin (0.6 microgram/kg). This method revealed the earliest stage of MCT, that is, multifocal hyperplasia of the C cells.

The earliest stages of MCT were found in the youngest family members and the results of total thyroidectomy were also most promising in those patients: 16 out of 19 patients with tumors less than 15 mm in diameter were considered radically cured as opposed to only 2 of 17 with larger and palpable tumors. At least 12 families with Sipple's syndrome live in Sweden. Six of these are either not at all or incompletely screened. To ensure adequate control of all individuals at risk of this genetic disease, a nationwide computerized register for the regular screening of members of these families is being prepared.

20. DIAGNOSIS AND TREATMENT OF FAMILIAL MEDULLARY THYROID CARCINOMA - NEW ASPECTS OF THE DISEASE

Emmertsen, K., Hansen, H. H., Nielsen, H. E., Mosekilde, L., Charles, P., Elbrond, O., Aarhus Kommunehospital, Dept. of Nuclear Medicine/Oncology & Radiation Therapy, *8000 Aarhus C, Denmark*

OBJECTIVES: 1. Diagnosis and treatment of familial medullary thyroid carcinoma (MCT). 2. Investigation of the effects on calcium-phosphorus metabolism of the raised S-iCT in patients with sporadic and familial MCT. 3. Investigation of the kinetics (secretion rate, volume of distribution, T 1/2 and renal clearance) of calcitonin in patients with MCT.

APPROACH: 1. The screening program will include determinations of basal and pentagastrin-stimulated serum immunoreactive calcitonin (S-iCT) as a tumor marker for MCT. Blood pressure and 24-hour urinary catecholamine excretion will be determined for diagnosis of possible pheochromocytomas. 2. a. Calcium metabolism is investigated by tracer kinetic methods. b. Bone structure is determined by histomorphometric analysis after tetracycline double labeling. c. Serum concentrations of parathyroid hormone and D-vitamins are determined by radioimmunoassay.

PROGRESS: 1. In one family, 5 patients have formerly been treated for MCT. Further, 6 patients have elevated basal and pentagastrin-stimulated S-iCT and are at present undergoing further evaluation. The screening program will be expanded to include the whole family. 2. b. Preliminary investigations have shown increased bone remodelling with increased numbers of osteoclasts and osteoblasts but reduced activity of these cells. c. Preliminary investigations have shown raised 1.25 dihydroxycholecalciferol concentrations in these patients. 3. This investigation is planned.

21. SCREENING RELATIVES OF PATIENTS WITH MEDULLARY CARCINOMA

Wells, S. A., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina,* 27710, United States of America

OBJECTIVES: Perform periodic screening of relatives of patients with medullary carcinoma of the thyroid using calcitonin radioimmunoassay. Provide accurate, sensitive, and specific measurements of immunoreactive calcitonin on samples of plasma or tissue from patients suspected of having medullary carcinoma of the thyroid. Radioimmunoassays will be performed as needed to screen subjects for the presence of disease, or to follow the clinical progress of disease treated by surgery or chemotherapy. The primary responsibility will be the measurement of samples obtained from patients followed in our MEN-II kindreds. Assay samples sent by other physicians in the southeastern United States if these physicians can provide basic clinical information on each patient. The information thus obtained may result in the discovery of new cases which might enter the study.

22. MONITORING FAMILIAL MEDULLARY CARCINOMA OF THE THYROID

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The syndrome of medullary carcinoma of the thyroid, pheochromocytoma and parathyroid gland hyperplasia or Multiple Endocrine Neoplasia Syndrome-Type II, is transmitted as an autosomal dominant trait with an approximate 50% chance of occurrence in children of an affected parent. In a large New Haven kindred, comprised of more than 120 members living in a close proximity to New Haven, annual screening of individuals 4 years of age and older has been performed for the past 4 years in the ambulatory facilities of the Adult (General) and Children's Clinical Research Centers, Yale-New Haven Medical Center. To December 1979, pentagastrin provocation, 0.5 mcg/kg and measurement of calcitonin by immunoassay was used as the screening procedure for medullary carcinoma. Positive re-

sponses were seen only in individuals previously known to have disease. As of 12/1/79 the procedure was altered to use a combined pentagastrin-calcium infusion based on the above recent data. Screening for parathyroid disease is performed simultaneously with the infusion using total and ionized calcium, alkaline phosphatase and immunoreactive parahormone levels. Urinary catecholamines are obtained on 24-hour collections and assayed in the laboratory of Dr. Lewis Landsberg, Beth Israel Hospital, for pre-symptomatic detection of pheochromocytoma.

Genetic analysis of the kindred performed during the year has succeeded in identifyiing one of the four main branches of the kindred as almost certainly not at risk based on absence of the disease through 4 generations and normal testing via pentagastrin provocation in more senior members of the branch. It is hoped that further analysis of the family pedigree using the clinical histories and responses to provocation will serve to eliminate other members of the family from active follow-up as 'at risk' for MEN Type II.

23. FAMILIAL INCIDENCE AND MULTIPLE MANIFESTATIONS OF MEDULLARY CARCINOMA OF THE THYROID

Williams, G. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine & Endocrinology Section, *820 S. Damen Ave., Chicago, Illinois,* 60612, United States of America

The purpose of this study continues to be to evaluate all family members of patients with diagnosed medullary carcinoma of the thyroid. This evaluation includes a) clinical evaluation, b) serum calcitonin by radioimmunoassay before and after calcium infusion, c) serum parathyroid hormone by radioimmunoassay, d) urinary catecholamine determination. In any patients in whom abnormalities are found, appropriate therapy will be carried out. In those subjects in whom the studies are normal, repeat studies will be done at 6 to 12 month intervals. In this way, this study should a) lead to early diagnosis and treatment of patients with medullary carcinoma of the thyroid before clinical manifestations are apparent, and b) yield additional information about the incidence, inheritance and natural history of this disease.

During the past year, 8 additional new patients suspected of medullary carcinoma of the thyroid have been evaluated, but the studies were normal in all of these patients. The one patient who was identified as a strong suspect for medullary carcinoma of the thyroid last year is in Europe and is not yet available for reevaluation. This patient will be more thoroughly investigated and family members will be evaluated as soon as she returns to this area.

This study continues.

24. PERIODIC SCREENING OF RELATIVES OF PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID USING CALCITONIN RADIOIMMUNOASSAY

Sizemore, G. W., Mayo Clinic, Dept. of Internal Medicine, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

OBJECTIVE: Determine the natural history of medullary carcinoma of the thyroid gland before and after early detection and therapy were made possible by measurement of plasma immunoreactive calcitonin. Establish the impact of systematic calcitonin screening and monitoring on the natural history of medullary carcinoma of the thyroid gland.

25. RADIATION-ASSOCIATED THYROID CARCINOMA

Shimaoka, K., Wallace, H. J., Roswell Park Memorial Inst., Dept. of Medicine, *666 Elm St., Buffalo, New York,* 14263, United States of America

A program has been instituted to screen annually by clinical and laboratory examinations those persons who have received radiation therapy to the head and neck areas for benign conditions. Those found to have goitre are further evaluated and treated by suppressive therapy with thyroid hormone. Those who respond are continued on long-term drug therapy, while those whose goitres increase in size are offered thyroidectomy. The natural history of radiation-associated benign and malignant thyroid diseases is being studied.

26. DETECTION OF MEDULLARY THYROID CANCER IN FAMILIES

Jackson, C. E., Tashjian, A. H., Kambouris, A. A., Henry Ford Hospital, Dept. of Medicine, *2799 W. Grand Blvd., Detroit, Michigan,* 48202, United States of America

Hereditary medullary carcinoma of the thyroid gland, a malignant neoplasm which is inherited as an autosomal dominant condition, is reliably detected by radioimmunoassay of calcitonin. The objectives of this study are to improve the methods of early detection of this neoplasm and to establish the optimum protocol for screening relatives of patients with medullary thyroid carcinoma. Amounts of calcitonin in plasma following various stimulation procedures will be measured in members of nine families already under investigation here and in members of the additional families of new index cases from this general area. Close clinical and laboratory follow-up of individuals in such families will be undertaken. Such information is important not only in providing the diagnosis of early disease, but also in establishing prognostic data on both treated and untreated individuals. Genetic linkage studies aimed at even earlier detection of this cancer will be conducted with these families and other kindreds at collaborating institutions. The principles and techniques of this study will be applied to the development of methods for early detection of lung cancer and other neoplasms in individuals at high risk.

27. SCREENING OF FAMILIAL MULTIPLE ENDOCRINE NEOPLASIA-TYPE II

Sisson, J. C., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Internal Medicine, *1335 E. Catherine St., Ann Arbor, Michigan,* 48104, United States of America

This is part of a broader project. A summary of this subproject is not available.

28. SCREENING OF THYROID PATIENTS WITH MEDULLARY CARCINOMA

Singer, F. R., University of Southern California, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

This is part of a broader project. A summary of this subproject is not available.

29. THYROID CANCER SCREENING - RECIPIENTS OF RADIATION THERAPY IN CHILDHOOD

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This is part of a broader project. A summary of this subproject is not available.

30. EARLY DIAGNOSIS OF MEDULLARY CARCINOMA OF THE THYROID IN MULTIPLE NEOPLASIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

B. DIAGNOSIS

1. IMMUNODIAGNOSTIC METHODS

31. IMMUNOLOGICAL REACTIONS IN CANCER OF MAN AND ANIMALS

Halliday, W. J., University of Queensland, Dept. of Microbiology, *St. Lucia, Brisbane, Queensland 4067, Australia*

OBJECTIVE: To study the leucocyte adherence inhibition test in man and experimental animals with regard to its mechanisms, specificity, and modification by serum factors, and to apply the test in immunological diagnosis and monitoring of human cancer.

APPROACH: The characteristics of the LAI test have been worked out with chemically induced tumors of mice, and shown to apply to natural tumors of men. It was anticipated that all tumors would have characteristic antigens, to which their hosts would respond consistently, and that these responses would be detectable in vitro.

PROGRESS: The LAI test has been shown to depend on the reaction between soluble tumor antigens and T-lymphocytes, with the liberation of a lymphokine (within 20 minutes) which diminishes the normal adherence to glass of macrophages or polymorphs. The kinetics of development of cell-mediated immunity to tumor antigens have been studied in mice, as have the phenomena of blocking and unblocking by serum factors. These parameters are determined with great regularity in human patients, notably those with melanoma, colon carcinoma and medullary carcinoma of thyroid. In human cancer the LAI specificity is related to tumor type. Well-defined patterns of reactivity are found in all stages of disease.

32. STUDY OF SERUM CEA AND CALCITONIN IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID

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OBJECTIVES: 1) To determine whether serum CEA is elevated in patients with medullary carcinoma of the thyroid. 2) To evaluate the use of serum CEA in diagnosis, monitoring the results of therapy and early diagnosis of metastases. 3) To establish whether determinations of serum CEA are as useful as determinations of serum calcitonin in diagnosis and monitoring of patients with MCT. 4) To determine whether serum CEA can be useful in screening for presence of disease in relatives of patients with the familial form of MCT.

APPROACH: 1) and 2) Determination of serum CEA by RIA in patients with histologically verified MCT. 3) Determination of serum calcitonin after calcium or pentagastrin infusions or both. 4) Determination of serum CEA in relatives of patients with familial MCT.

PROGRESS: 1) Serum CEA is raised in patients with MCT and is not elevated in other forms of thyroid carcinoma. 2) Serum CEA appears to be a good tumor marker for MCT. 3) Serum CEA in most cases can be correlated with serum calcitonin levels.

Work is still in progress on 2), 3) and 4) of APPROACH.

33. IMMUNOASSAY OF CALCITONIN

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We are pursuing our studies of the pathophysiology of calcitonin, utilizing the radioimmunoassay we have developed for the hormone in serum and urine.

The newest tool in our armamentarium to study calcitonin pathophysiology is a specific, sensitive radioimmunoassay to measure calcitonin in the urine. This assay is simple, reproducible and allows for removal of interfering substances which complicate the serum assay. We have found this test extremely useful in the evaluation of patients with medullary thyroid cancer. Many patients, with normal basal serum calcitonin, have high urinary calcitonin.

We have found that calcitonin persists in the blood and urine of totally thyroidectomized humans. In an autopsy study, we find that calcitonin has a widespread distribution in many tissues other than the thyroid gland. We have recently completed an experiment in which we have shown that the extrathyroidal tissues of monkeys continue to contain large amounts of calcitonin two months following total thyroidectomy. The demonstration of extrathyroidal calcitonin may explain why thyroidectomy is not associated with any profound changes in calcium or phosphate metabolism. Pulmonary calcitonin has been localized to the bronchiolar Kultschitzky cell by immunoperoxidase staining. In patients with pneumonia, serum and urine calcitonin are elevated during the acute phase and decrease as the inflammation subsides. Pneumonitis must be considered as a cause for hypercalcitonemia, especially when calcitonin is being used as a marker for bronchogenic cancer.

34. CARCINOMA OF THE THYROID - SERUM THYROGLOBULIN AS A MARKER FOR METASTASES

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OBJECTIVES: (1) Establishment of a radioimmunioassay (RIA) for human thyroglobulin (Htg) and determination of normal ranges. (2) A follow-up study of approximately 180 patients with thyroid carcinoma -the total number diagnosed in this province between 1955 and 1975. An evaluation of serum thyroglobulin as a marker for recurrent or metastatic cancer of the thyroid will be included in the clinical and laboratory assessment of these patients and also in (3) a prospective study of all newly diagnosed patients with cancer of the thyroid.

PROGRESS: Normal range - 0-25 ng/ml. Results in an initial group of patients are being carefully rechecked and compared with values from another center. Approximately two-thirds of all pathology specimens have been reviewed. More nearly uniform protocols are being worked out with pathologists, surgeons, radiotherapists and other physicians.

35. THYROGLOBULIN RADIOIMMUNOASSAY IN THYROID CARCINOMA

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Clinical studies correlating active well differentiated thyroid carcinoma with circulating levels of human thyroglobulin (Htg) by radioimmunoassay suggest that the latter could conceivably replace other procedures, e.g., total body scans, as an effective method of patient evaluation. In a prospective cross-sectional study, 90% of patients post-thyroidectomy and post-131I ablation who have Htg levels less than 7 ng/ml, have negative total body scans, whereas 100% of those patients with values greater than 7mg/ml, have positive scans showing evidence of residual tumor or normal thyroid tissue. The 10% of patients with positive scans and Htg levels less than 7ng/ml most likely have normal residual thyroid tissue since no evidence of metastases or residual tumor has been obtained. Chi square analysis of these data indicate that Htg levels accurately reflect total body thyroid scans (p less than .001). No longitudinal data using Htg have been reported and it is likely but unproven that Htg levels will be similarly effective. These data are important since they may provide an earlier diagnosis of tumor recurrence with associated earlier therapy. A longitudinal prospective study is proposed to assess the onset of metastases by total body scans compared to serum Htg levels. Total body thyroid scanning will be performed on a yearly basis for five years, whereas Htg levels will be determined with clinical examinations every six months for five years. These data should indicate whether Htg levels are more sensitive and/or specific than currently existing techniques and whether or not the Htg levels can replace this technique. Htg from tumor and normal thyroid tissue is immunologically identical; however, there are chemical and physical differences. Normal and tumor Htg will be purified and analyzed by a number of techniques. These forms of Htg will be assessed to evaluate circulating species of Htg that may be tumor markers. Thus, the goal of presurgical diagnosis of thyroid carcinoma is conceivable. The cost effective implications of preoperative diagnosis and improved longitudinal evaluation will have a major impact upon health care delivery in this country.

36. ORGAN SPECIFIC TUMOR LOCALIZING ANTIBODY

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Much human cancer originates in organs not vital to the life and well-being of the patient. Many of these malignant tumors retain to some extent the morphological and histological characteristics of the organs or tissues from which they are derived. We believe that such tumor cells are also likely to retain the antigenic characteristics of some of the normal cells of the tissues that underwent malignant change. If such an antigen is expressed on the surfaces of tumor cells, but not on cells vital to the life and well-being of the patient, this antigenic characteristic may provide a target for an attack on tumor by immunological mechanisms.

We are looking for such antigens in rats, by trying to prepare radioactive antibodies able, after i.v. injection, to localize with high specificity in tumors originating in mammary

tissue, large intestine, pancreas, and thyroid tissue. Antibodies will be sought in xenogeneic antisera. Radioactive tumor localizing antibody will be used as an immunological probe to identify the corresponding antigens during tumor cell fractionation studies. Such isolated antigens will then be used as immunogens to produce sera containing a larger fraction of tumor localizing antibody.

2. OTHER DIAGNOSTIC METHODS

37. ULTRASTRUCTURAL STUDIES OF BENIGN AND MALIGNANT HUMAN THYROID TUMORS

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OBJECTIVE: To determine whether we can separate the benign thyroid tumors derived from the follicular epithelium from the malignant ones, by using transmission and scanning electron microscopy in conjunction with morphometry and DNA flow cytophotometry.

APPROACH: I have, during the past 6 years, collected several hundred specimens from human thyroid tumors. Most of the specimens have been secured for histopathology, cytology, transmission electron microscopy, scanning electron microscopy as well as histochemistry and DNA flow cytophotometry. The investigation aims to clarify whether there are diagnostically useful differences in the benign and malignant follicular thyroid tumors, as a proper classification may sometimes be impossible by light microscopy when no metastases are present.

The investigation furthermore aims to determine whether the follicular areas of papillary thyroid carcinomas are similar to follicular carcinomas or papillary ones, to determine whether the classification into mixed follicular and papillary carcinomas of the thyroid should be sustained or omitted. This not only has prognostic implications but also epidemiological ones, as some investigators now classify mixed tumors as such, while others classify them as papillary carcinomas, while still others classify follicular tumors with ground glass nuclei as papillary carcinomas.

PROGRESS: The work on the material has already started and preliminary results been published.

BIBLIOGRAPHIC REFERENCES: Johannessen, J.V., Gould, V.E., Jao, W.: The fine structure of human thyroid cancer. Hum. Pathol. 9, 385-400, 1978; and Gould, V.E., Johannessen, J. V. and Sobrinho Simoes, M.A.: The Thyroid Gland in Electron Microscopy in Human Medicine, Vol. 10, Endocrine Organs (ed. J.V. Johannessen), McGraw-Hill International Book Company, New York, 1980, in press.

38. CELL SEPARATION AND KINETICS PROGRAM

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The purpose of this project is to identify, during surgery, hyperplasia in normal-appearing parathyroid glands with the technique of flow cytometry (FCM) and to correlate these findings with the clinical course of patients postoperatively. The specific objectives of the parathyroid study are as follows:

OBJECTIVE 1: FCM evaluation of hyperplasia in normal, 'normal' and adenomatous parathyroids.

This objective is an extension of our ongoing study that now includes over 46 patients. In this study, flow cytometric techniques are used to classify biopsied parathyroid tissue into normal and adenomatous groups for patients undergoing parathyroidectomy for hyperparathyroidism.

OBJECTIVE 2: FCM evaluation of DNA and protein content in normal, 'normal' and adenomatous parathyroids.

It is the purpose of this objective to measure simultaneously DNA content (hyperplasia marker) and protein content (hyperfunctioning marker) with a two color flow cytometer. The measurement of protein should theoretically increase the sensitivity of this assay system.

39. STUDIES IN THYROID DISEASE

Robbins, J., Weintraub, B. D., Pretorius, H. T., Fein, H., Fradkin, J., Chu, E. W., Brennan, M., Jones, A. E., Line, B., Aamodt, R., Schneider, A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Arthritis, Metabolism & Digestive Diseases, Endocrine Physiology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

In the diagnosis of thyroid nodules and goiter, further data have been accumulated on the utility of fine needle aspiration cytology in preoperative diagnosis. This has also been an effective means of diagnosing lymphocytic thyroiditis. In the treatment of thyroid cancer, the serum thyroglobulin levels are being evaluated in correlation with the previously completed study of whole body 131I scanning. The method promises to be useful provided that patients are allowed to become at least mildly hypothyroid. In the treatment of hyperthyroidism, it was found that both iodide and lithium are effective in controlling hyperthyroidism after the use of relatively low dose 131I therapy. In the amounts used, iodide produced a greater response than lithium. In the syndrome of inappropriate secretion of thyrotropin (TSH), iodothyronine metabolism was studied in two patients. The metabolic clearance of T4 and T3 was low relative to their circulating hormone levels, but the conversion of T4 to T3 was not impaired. This suggests a possible defect in the entry of thyroid hormones into cells. In the syndrome of postpartum thyroiditis with transient hypothyroidism, several additional patients have been detected and studied.

BIBLIOGRAPHIC REFERENCES: Goldman, J., Line, B., Aamodt, R., and Robbins, J.: Influence of triiodothyronine withdrawal time on 131I uptake post-thyroidectomy for thyroid cancer. J. Clin. Endo. Metab. 50: 734-739, 1980. Robbins, J., Rall, J. E., and Gorden, P.: In Bondy, P. K., and Rosenberg, L. E. (Eds.): Metabolic Control and Disease, 8th Edition. W. B. Saunders, Philadelphia, 1980, pp. 1325-1425.

40. THYROID NEEDLE BIOPSY - THYROID CANCER DIAGNOSIS

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This is part of a broader project. A summary of this subproject is not available.

41. DIGITAL COMPUTER IN SCINTIGRAPHY OF TUMORS

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OBJECTIVE: The aim of the study is to improve the results of tumor scanning by use of a digital computer.

APPROACH: Structures within static images are automatically separated, quantitated, and their content expressed in various modes: (I) A known fraction of the administered dose (standard) can be included into the scanning field and results presented either as (1) percentage of the dose within a structure or as (2) a quantitative image where the symbols designate concentration in percentage of doses/cm2 of the image. (II) Alternatively, the 'body background' can be determined and a similar quantitative image produced in terms of target/non-target ratios.

PROGRESS: These techniques proved to be useful in quantitating 67-Ga uptake in thyroid tumors and are currenty used for in vivo cell cycle studies in 'synchronized' oropharyngeal carcinomas with 99m-Tc bleomycin. Tumor uptake of radiopharmaceuticals can be quantitated and followed after therapy (131-I, 67-Ga). The detection power of tumor-seeking agents can be compared (18-F/85-Sr). Subtraction of dual tracer records can be performed better by computer than by analogue circuitry.

42. USE OF RADIOACTIVE PHOSPHORUS IN EARLY DIAGNOSIS OF RECURRENT CARCINOMA OF THE HEAD AND NECK

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This project continues and we now use bleomycin-EDTA (BLEDTA) tagged with indium III. We have studied 60 head and neck squamous cell cancer patients to date who have had BLEDTA injections. The tumors ranged in size from 0.6 cm to 8 cm. We have found an 85 percent positive scan rate - the false negatives being seen with the smaller tumors. Positive scans

have also been seen in thyroid adenocarcinoma and pulmonary tuberculosis.

43. FLUORESCENCE SCANNING IN THYROID CANCER

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This is part of a broader project. A summary of this subproject is not available.

44. DETECTION OF NECK THYROID REMNANT OR METASTASIS AFTER NECK ABLATION (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

C. PATHOPHYSIOLOGY

45. STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

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Our main activity involves the study of the hormone calcitonin. We are currently exploring the physio-chemical state of calcitonin in the blood. We have developed a sensitive radioreceptor assay for the hormone, in order to determine which of the heterogenous serum fractions react with receptor. We have also developed a radioimmunoassay for calcitonin in the urine, and have found it to be of considerable value in the diagnosis of medullary thyroid cancer. We have determined urine calcitonin in normal children ages 2-15 years; children up to age 13 have higher values than adults. Children undergoing a diagnosis of medullary thyroid cancer must be compared by sex and age. In addition, we are utilizing serum and urinary calcitonin as a label for lung cancer and breast cancer.

We have found that large amounts of calcitonin exist in several tissues other than the thyroid gland; the gel filtration of this extrathyroidal calcitonin is identical to the monomer. In exploring its presence in muscle we have found that exercise induces a change in the excretion pattern of urinary calcitonin. In our study of pulmonary calcitonin we have localized calcitonin in the Kultschitzky cell of the lung by immunoperoxidase staining. We are pursuing our studies of muscle and lung calcitonin.

46. HORMONE-PRODUCING TUMORS - IN VIVO AND IN VITRO STUDIES OF GROWTH AND FUNCTION

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This research proposal is designed to study in vitro and in vivo the growth and function of tumors associated with abnormal plasma calcitonin levels. Calcitonin will be measured in blood, tissue culture medium, and tissue specimens by radioimmunoassay and immunohistological procedures in combination with biochemical and immunochemical methods. Measurements will also be made of apparently related hormones such as ACTH and beta endorphin. The in vivo studies will be performed in patients with hypercalcitoninemia and malignancy, including medullary thyroid carcinoma and oat-cell carcinoma of the lung and other neural crest tumors, and in a rat model of a transplantable medullary thyroid carcinoma. Calcitonin measurements will be made in the basal state and during provocative tests of secretion and during therapeutic regimens. The in vitro studies will be performed with monolayer tissue cultures of calcitonin-producing cells from animal and human tumors. These studies will be designed to investigate the basic biological processes of the cells such as growth and hormone biosynthesis and secretion and to identify factors which regulate these processes. Attempts will be made to establish cell lines of these tumors. The normal counterparts of these malignant cells will also be studied for comparison. These studies will be designed to elucidate the pathogenesis of the hypercalcitoninemia of malignancy. This should result in the further development of clinically useful procedures for the early diagnosis and management of patients with these tumors. This project should thus provide both basic and clinical information about hypercalcitoninemia and cancer.

47. C-CELL HYPERPLASIA AND MEDULLARY CARCINOMA OF THE THYROID

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The syndrome of familial medullary thyroid carcinoma is inherited as an autosomal dominant trait and is characterized by the development of bilateral and multicentric C-cell and adrenal medullary tumors. Sequential clinical screening studies for determination of calcitonin and catecholamine levels in these kindreds, combined with correlative pathological analyses, have led to the concept that both these tumors are preceded by relatively long pre-neoplastic phases of C-cell and adrenal medullary hyperplasia. The human tumor system, together with similar experimental animal models, provides an opportunity to study the early phases of neoplastic growth and to delineate the differences between physiological and pre-neoplastic (pathological) hyperplasia in vivo and in vitro. Alterations in cell junctions (desmosomes), abnormalities in the basal lamina, and heterogeneity in secretory granule morphology will be correlated with tissue and serum calcitonin heterogeneity and other peptide hormone production by radioimmunoassay, immunocytochemistry and morphometric analyses, with the progressive phases of pre-neoplastic and neoplastic development. In vitro studies of the effects of various agents on modulation of peptide hormone synthesis and secretion will be undertaken in normal, hyperplastic and neoplastic cells.

BIBLIOGRAPHIC REFERENCES: Wolfe, H.J., DeLellis, R.A., O'Briain, D.S. and Tashjian, A.H., Jr. Immunocytochemical localization of calcitonin-like material in the pituitary gland. Lab. Invest., 40:292a, 1979. Dayal, Y., O'Briain, D.S. and Wolfe, H.J. SRIF- and G-cell hyperplasia in duodenal ulcer disease: A morphometric study. Lab. Invest., 40:251a, 1979.

48. STUDY OF THE PHYSIOLOGICAL FUNCTION AND HISTOLOGICAL CHANGES OF THYROIDS IRRADIATED WITH RADIOACTIVE IODINE

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The objective is to study the effects of radioiodines on the thyroids of man and animals, with special emphasis on the latent effects, whether from fallout or from diagnostic or therapeutic use. The behavior of therapeutic doses of radioiodine will be examined in man when the radioiodine is given, and later the thyroid failure and the ultimate failure of cell replication will be studied. The development of tumors in patients previously so treated or in the Marshallese who have been developing tumors from radioiodines in fallout will also be studied. The small doses of 131-I which produce tumors in the thyroid will be explored in animals (rats) and the nature of those tumors will be studied, with special attention to the nature of their evolution. An experimental model has been discovered in rats which produces a high incidence of tumors. The inception and sequence of development of the tumors has been explored. Much has been learned of how the tumors evolve. A high incidence of breast tumors has been found incidentally in these irradiated rats. This is to be explored further. New cases of thyroid tumors are found in the course of studies in the exposed Marshallese each year.

49. STUDY OF EVENTUAL ALTERATIONS OF THYROID FUNCTION IN THE IRRADIATION OF HEAD AND NECK TUMORS

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OBJECTIVE: To study thyroid function in patients with head and neck tumors in whom the thyroid was included in the irradiation field. High energy equipment (4 MeV Linear Accelerator) was used with a dose of 5,000 rads in 5 weeks with an average T.D.F. of 82.

METHOD: The assessment of thyroid function is performed through uptake, scanning, T3 retention and T4 saturation tests before and after radiotherapy, as well as 3 months after the end of treatment.

50. TUMOROUS AND NONTUMOROUS CELLULAR SITE OF LOCATION OF RADIOPHARMACEUTICALS

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The purpose of this project was to elucidate the exact cellular site of localization of various radiopharmaceuticals in normal, tumorous, and nontumorous conditions. During the past year, work has progressed in light microscope autoradiography to study the differences in intrathyroidal site of concentration of two thyroid imaging agents, namely, Tc-99m-sodium pertechnetate and I-131-sodium iodide in normal rat thyroid gland. Ten Sprague-Dawley male rats (150-250 gm), fed Purina laboratory chow were used. Five rats in each group received i.p. 5-10 microcuries Tc-99m-pertechnetate or 50-100 microcuries I-131-iodide. Following sacrifice of animals at 1/2-24 hours post-injection, the thyroid was removed, frozen in isopentane, cooled in liquid nitrogen, and sectioned (2-4 microns) in a cryostat. The frozen sections were then placed directly on to the slides coated with Kodak NTB 3 nuclear track emulsion, and were exposed at minus 30 degrees C for 1-7 days in a light-tight box. The slides were then developed, fixed, stained, and examined under the light microscope. Control autoradiographs were prepared with non-radioactive thyroid sections to rule out positive or negative chemographic effects. These studies demonstrated a major concentration of pertechnetate in the follicular cells with little activity in the lumens of the follicle, while iodide grains concentrated predominantly in the colloid. Thus, there is a basic difference in the cellular site of localization of pertechnetate and iodide by the thyroid gland which may explain the often noticed discrepancy in the thyroid studies performed with these two isotopes. This work has been published in Fed. Proc. Vol. 39:947, 1980.

51. EPIDEMIOLOGY AND HISTOLOGICAL AND ELECTRON-MICROSCOPIC DIAGNOSIS OF THYROID CANCER - IODINE PROPHYLAXIS

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OBJECTIVE: To study endemic goiter, particularly with regard to a systematic iodine prophylaxis by means of iodinizing salt, established in 1960.

APPROACH AND PROGRESS: In the Swiss endemic goiter area an analogous salt prophylaxis was introduced about 30 years ago. In this tumor material some interesting changes in morphology and clinical behavior have been noticed, and the results published.

We revised our histological tumor material from the years 1952-1975 and classified the specimens according to the WHO schedule, using uniform criteria. The exact morphological diagnosis (including number of infiltrations of the tumour capsule and blood vessels) was correlated with the clinical course of the disease. The total number of reclassified carcinomas was 453.

Furthermore we studied the epidemiological criteria of these carcinomas (sex, age, incidence) in contrast to the 10423 non-malignant thyroid tumors. In order to determine the value of diagnostic improvement influencing the morphological pattern of thyroid tumors, we studied the preoperative clinical findings of the non-malignant thyroid tumors (symptoms, radiology, scintigrams, cytology) and correlated these data with the morphological features (weight, macroscopy, histology). For selected years (before and after the introduction of iodine prophylaxis) we studied the lymphocytic infiltration of the thyroid specimens and found a severe increase in this alteration after iodine prophylaxis. To evaluate this dependency of the morphology and biology of thyroid neoplasms on the specific endocrine situation we studied 25 thyroid carcinomas by means of electron microscopy. In differentiated carcinomas we often found disorganization of cytoplasmic organelles such as hyperplasia or hypertrophia of a single organelle type (mitochondria, lysosomes, rough and smooth ER, cytoplasmic vesicles). These findings will allow us to study the physiologic function of the respective cytoplasmic organelles.

52. BIOLOGIC CHARACTERISTICS OF THYROID CANCER

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This study is designed to evaluate (1) the effect of thyrotropin suppression in nodular goiter and thyroid cancer, (2) factors influencing survivorship in patients with thyroid cancer, (3) improved diagnostic methods to distinguish between cancer and benign thyroid disease, and to characterize qualitatively and quantitatively (4) TSH receptors in normal and pathologic human thyroid tissue.

53. THE UNIVERSITY OF CHICAGO CANCER RESEARCH CENTER (UCCRC) - LYMPHOMALEUKEMIA CLINICAL RESEARCH PROGRAM

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The University of Chicago Cancer Research Center: Clinical Cancer Research Program is a multidisciplinary research effort encompassing diagnosis, staging, treatment, and correlations with basic science investigations in the following broad areas: (1) Breast Cancer -Pathologic evaluation of cases and correlation with estrogen receptors, lymph node morphology, and endocrine data will be continued; antibodies to receptor protein have been prepared and efforts to develop a radioimmunoassay will continue. (2) Gastrointestinal Cancer - The program to assess vulnerability of ulcerative colitis patients to cancer continues employing histologic and cytologic assessment with colonoscopy as well as studies of humoral and cell-mediated immunity. (3) Thyroid Cancer - Comparison of irradiated patients and patients who had thyroid carcinoma without history of irradiation continues. The immunologic status of thyroid cancer patients is being evaluated. TSH receptors on the surface of thyroid tumors will be studied. Immune complexes are being determined in the circulation of the patients. (4) Comprehensive Approach to Glioma Therapy - Kirsten virus induced brain tumors in rats are employed to study pathogenesis and test radio/chemotherapeutic interventions. A study of combined surgery, radiotherapy and chemotherapy with BCNU and epipodophyllotoxin is being completed. Glia maturation factor has been purified to homogeneity and specific antiserum is being obtained. (5) Lymphoma-Leukemia Program - Sensitive cellular assays measuring nanogram quantities of Ig have been developed to study B-cell function; T-cell cytotoxicity can also be assayed accurately. These techniques are used to study neoplastic lymphocytes. The project encompasses a determination of surface T- and B-cell markers, a cytogenetic analysis, the measurement and functional role of autologous serum immune complexes, and the determination of the effects of alpha-fetoprotein, an oncofetal protein, on the neoplastic cells contained in these separate lymphocytic malignancies.

54. PARATHYROID FUNCTION AFTER PARATHYROID ADENOMA RESECTION (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

55. LOCALIZATION OF ANTI-CEA ANTIBODY WITH MEDULLARY THYROID CARCINOMA

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This is part of a broader project. A summary of this subproject is not available.

56. OUT-PATIENT STUDIES OF PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID GLAND

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This is part of a broader project. A summary of this subproject is not available.

57. MEDULLARY THYROID CARCINOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

D. THERAPY

58. TOTAL THYROIDECTOMY FOR CANCER OF THE THYROID

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This series was started in 1965 according to a protocol designed to determine the incidence of multicentricity of thyroid carcinoma and the potential beneficial effect of total thyroidectomy in reducing long-term tumor recurrence rates and mortality as compared to other long-term series where only a lobectomy was performed.

Since total thyroidectomy has a potential of an increased rate of recurrent nerve palsy and permanent hypoparathyroidism, the benefits of total thyroidectomy must be evaluated in terms of this added risk.

During the past year, 15 patients were added to this series, which now totals 135 patients. The incidence of multicentricity (bilaterality) stands at approximately 40%. The incidence of hypoparathyroidism (permanent) is less than 1%. This is probably due to our long standing utilization of parathyroid autotransplantation, when the vascular supply of these glands is compromised. The rate of recurrent nerve palsy is less than 1.3%.

BIBLIOGRAPHIC REFERENCES: Paloyan, E., Lawrence, A.M.: Thyroid Neoplasms after Radiation Therapy for Adolescent Acne Vulgaris. Arch. Dermatol. 114:53-55, Jan. 1978. Braithwaite, S.S., Orfei, E., Moran, J.M. and Paloyan, E.: Metastatic Thyroid Carcinoma in Myxedema. (Letter to the Editor) Arch. Intern. Med., 140:282, Feb. 1980.

59. MANAGEMENT OF PATIENTS WITH A HISTORY OF IRRADIATION TO THE THYROID GLAND

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This series began in 1965 according to a protocol designed to determine the incidence of occult malignancies, bilaterality of cancers, and the potential long term, beneficial effects of otal thyroidectomy (in spite of added risks of permanent hypoparathyroidism and recurrent nerve palsy) in patients with thyroid nodules and a history of exposure to head and neck irradiation for benign diseases.

During the past year, 22 patients were added to this series, which now numbers 167. The incidence of carcinoma is approximately 43%, the incidence of multicentricity 40%, figures which are similar to our previous reports. A significant malignancy would have been overlooked in 6 patients, if total thyroidectomy had not been done. The incidence of permanent hypoparathyroidism and recurrent nerve palsy still stands at approximately 1%.

BIBLIOGRAPHIC REFERENCES: Paloyan, E. and Lawrence, A.M.: Thyroid neoplasms after radiation therapy for adolescent acne vulgaris. Arch. Dermatol. 114: 53-55, Jan. 1978. Paloyan, E., Prinz, Richard A., and Lawrence, Ann M.: Current Trends in Endocrine Surgery. Surgery Annual 12:205-222, 1980.

60. RADIATION-INDUCED THYROID CANCER

Schneider, A. B., Frohman, L., Pinsky, S., University of Chicago, Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

The major objective of this research proposal is to study radiation-induced thyroid cancer by a coordinated program of clinical and basic endocrinological investigations. The clinical studies are designed to determine the current risk and continuing incidence of radiation-induced thyroid cancer and to evaluate methods of diagnosis and medical and surgical approaches to treatment. This will be accomplished by a longitudinal study of patients who have been evaluated at Michael Reese Hospital because of a history of childhood head or neck irradiation. Of 5,200 patients who were so treated, 1,700 have been examined and another 1,400 have been contacted. In this population there is a 32% prevalence of nodules and among those who have had surgery 36% have had thyroid cancer. Follow-up examination of patients who were initially normal will provide an estimate of the continuing incidence of radiation-induced thyroid cancer. Follow-up examination of patients who were initially abnormal will provide an evaluation of the various methods of treatment which have been used. Together these will provide the information necessary to develop clinical guidelines for the care of persons with a history of head or neck irradiation.

Laboratory studies will focus on the role of plasma thyroglobulin in the diagnosis of thyroid tumors. Plasma thyroglobulin is elevated in a majority of patients with thyroid nodules and in 12% of patients who have a history of irradiation but who otherwise appear completely normal. This project will determine whether an elevated thyroglobulin level indicates an especially high risk for the formation of thyroid nodules.

We will continue our detailed studies of the molecular properties of plasma thyroglobulin using physical-chemical methods in order to improve its diagnostic usefulness and to understand how it enters the circulation. The Wollman transplantable thyroid tumor line 1-1C2 will be used as a model system for the study of plasma thyroglobulin and thyroid cancer.

BIBLIOGRAPHIC REFERENCES: Schneider, A.B., Stachura, M.E., Arnold, J., Arnold, M., and Frohman, L.A.: Incidence, Prevalence and Characteristics of Radiation Induced Thyroid Tumors. American Journal of Medicine. 64:243-252, 1978. Schneider, A.B., and Pervos, R.: Radioimmunoassay of Human Thyroglobulin: Effect of Antithyroglobulin Autoantibodies. Journal of Clinical Endocrinology and Metabolism 47:126-137, 1978.

61. MEDULLARY CARCINOMA OF THE THYROID (HUMAN)

Reichlin, S., New England Medical Center Hospital, *171 Harrison Ave., Boston, Massachusetts*, 02111, United States of America

This is part of a broader project. A summary of this subproject is not available.

62. USE OF BROMOCRIPTINE (CB-154) IN MEDULLARY THYROID CARCINOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

III. ADRENAL TUMORS

63. EVALUATION OF CT BODY SCANNING IN ONCOLOGIC PATIENTS

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OBJECTIVES: To compare CT scanning with other imaging modalities in the detection and follow-up of tumors. To extend our ability to image malignancies at presentation for staging purposes as well as to demonstrate followable disease.

METHODS EMPLOYED: CT is performed as a staging modality as well as at periodic follow-up intervals. Currently, patients with malignant lymphomas, ovarian carcinoma, malignant melanoma, testicular tumors, adrenal carcinomas, prostate carcinomas, oat cell carcinoma of the lung, and a variety of soft tissue sarcomas are being studied most intensively.

BIBLIOGRAPHIC REFERENCES: Dunnick NR, Schaner EG, Doppman JL, Strott CA, Gill JR and Javadpour N: CT in Adrenal Tumors. Am. J. Roentgenol. 132:43-46, 1979. Dunnick NR, Schaner EG and Doppman JL: Detection of Subcutaneous Metastases by CT. J. Comput. Assit. Tomogr. 2:275-279, 1978.

64. DEVELOPMENT OF TUMOR AND ORGAN IMAGING AGENTS

Spitznagle, L. A., Marino, C. A., Kasina, S., University of Maryland, Baltimore Professional Schools, School of Pharmacy,

Dept. of Medicinal Chemistry/Pharmacognosy, *1420 N. Charles St., Baltimore, Maryland,* 21201, United States of America

This proposal deals with the design and preparation of radiopharmoceuticals potentially useful for imaging tumors of steroid target organs such as the adrenal, mammary and prostate glands. Thin-layer chromatography, high pressure liquid chromatography and nuclear magnetic resonance spectroscopy will be used to purify, identify and quantitate the proposed agents. The kinetics of distribution of the F-18 labeled agents will be studied in experimental animals in order to obtain the information necessary to allow their evaluation as potential radiopharmaceuticals for imaging steroid target organs.

BIBLIOGRAPHIC REFERENCES: Spitznagle, L.A., Marino, C.A., and Eng, R.R., 1980. The use of a Crown Ether to synthesize a Fluorine-18 Labeled Steroid. Chapter in: Frontiers In Nuclear Medicine, Springer-Verlag, Heidelberg, (in press). Spitznagle, L.A., Spencer, R.P., and Jay, M. 1980: Factors Influencing Radiopharmaceutical Distribution. Chapter in Radiopharmaceuticals: Structure-Activity Relationships. Grune and Stratton Company (in press).

65. VISUALIZATION OF ADRENAL ABNORMALITIES USING 131I-6-IODO-METHYL-19NORCHOLESTEROL (131I-IODOCHOLESTEROL)

Polcyn, R. E., Lieberman, L. M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine Service, *2500 Overlook Ter., Madison, Wisconsin,* 53705, United States of America

PROJECT OBJECTIVES: To provide anatomical and functional information about the adrenal glands in patients with clinical and biochemical evidence of unilateral or bilateral hyperfunction.

PLAN: An Investigational New Drug Application (IND) has been obtained from the Food and Drug Administration (FDA) to use 131I-iodocholesterol at the University of Wisconsin Hospital and Clinics and the Middleton Memorial Veterans Hospital. The radiopharmaceutical is available from the University of Michigan Department of Nuclear Pharmacy under an approved IND. Following IV injections of 131I-iodocholesterol we will study patients with a gamma camera or tomographic scanner.

METHOD: One mCi/1.73 m2 of body surface area will be given IV to patients. All patients will receive stable iodine by mouth two days before the dose of radiopharmaceutical. In selected patients, Dexamethasone suppression may be given 5-7 days before the scan procedure. Seventy-two hours after dose, the patient will be imaged with a gamma camera or tomographic scanner and the study repeated four days later.

RESULTS TO DATE: Over thirty patients have been studied with very good clinical correlation. One patient with unsuspected adrenal carcinoma was identified and a second patient confirmed. All patients with adrenal adenoma have been identified. Only one patient thought to have a benign hyperfunctioning adenoma was a false positive study. The need for adrenal venography was avoided in a number of patients because of the non-invasive nuclear medicine procedure.

66. CATECHOLAMINE METABOLISM IN FAMILIAL PHEOCHROMOCYTOMA

Atuk, N. O., Westfall, T. C., University of Virginia, School of Medicine, Dept. of Medicine, *Box 246, Charlottesville, Virginia,* 22901, United States of America

OBJECTIVE: The investigation of the mechanism of normal blood pressure and the aging process in patient and familial pheochromocytoma. This project includes: a) Platelet uptake of catecholamines; b) COMT and MAO activity, RBC and tumor tissue; c) pressor responsiveness to I.V. NE infusion; and d) autonomic nervous system evaluation of these patients and control subjects.

67. 24-HOUR PLASMA CORTISOL PROFILES TO DISTINGUISH CUSHING'S SYNDROME

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This is part of a broader project. A summary of this subproject is not available.

IV. PANCREATIC TUMORS

A. DIAGNOSIS

1. IMMUNODIAGNOSTIC METHODS

68. DIAGNOSIS OF CANCER OF THE PANCREAS - INTERACTION BETWEEN PROTEASES AND PROTEASE INHIBITORS IN MALIGNANT DISEASE (ABBREV)

Ohlsson, K., Borgstrom, A., Genell, S., Tegner, H., Marks, W., Malmo General Hospital, Dept. of Surgery, *S Forstadsgatan 101, S21401 Malmo, Sweden*

The biochemical pattern of cancer of the pancreas: We aim primarily at developing and expanding our immunochemical methods for the analysis of proteins secreted by the pancreas in both juice and plasma. These methods will be tested in a clinical program dealing with cancer of the pancreas with the purpose of trying to evolve simple methods which can make possible an early diagnosis. Corresponding methods will be developed for the secretory proteins of rat pancreas. They will be evaluated in model studies of acinar cell injury and cancer induction.

A survey of the content of neutral proteases in cancer of the colon and the interaction with endogenous protease inhibitors: Preliminary results indicate the existence of collagenolytic activity in cancer of the colon. Our aim is to attempt to isolate the responsible enzyme in order to characterize and prepare an antiserum.

Studies dealing with the occurrence of the so-called bronchial inhibitor in normal plasma as well as in the case of inflammatory and neoplastic processes in the upper respiratory tract or in the genital tract: We have already produced a specific antiserum against the inhibitor and intend as an initial step to develop an RIA-method, which permits quantitation of the inhibitor at a level of 1 microgram/l.

Quantitative and qualitative studies of collagenase and elastase from neutrophilic granulocytes and their inhibitors in plasma in acute leukemia: Our specific antisera against proteases as well as inhibitors make an immunochemical approach possible. The results obtained shall provide a basis for future analyses of possible harmful effects of these enzymes in cases of leukemia.

69. IMMUNODIAGNOSIS OF PANCREATIC CANCER

Douglass, H. O., Goldrosen, M. H., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

Leukocytes from a total of 212 patients have been assayed against an antigen derived from pancreatic adenocarcinoma. Results, to date, have indicated that the leukocytes from 11 of 12 patients whose cancers are localized or confined to lymph nodes adjacent to the pancreas have identified the antigen, whereas leukocytes in 6 of 9 patients with more distant lymph node involvement have identified that antigen. Among patients with metastatic pancreatic carcinoma with either intra-abdominal spread or hematogenous spread to organs other than the liver, leukocytes from 10 of 12 patients have identified the antigen. In contrast, leukocytes from only 15 of 27 patients with metastatic pancreatic adenocarcinoma of the liver have identified these antigens. There have been no false positives among the 17 patients with pancreatitis, 2 false positives among 16 patients with other diseases of the gastrointestinal tract and one false positive among 30 normal healthy controls. Among patients with carcinoma, there have been 2 false positives in the group of 71 patients with gastrointestinal tract cancer (both had cholangiocarcinoma) and 2 other false positives in the group of 18 patients with carcinomas of other than gastrointestinal origin. Preliminary studies evaluating serum 'arming' of normal healthy leukocytes and the use of those 'armed' leukocytes in LAI have shown concordant results in 76% of tests thus far. Further studies are under way to assess the value of 'arming' and seek standardization of an antigen source.

BIBLIOGRAPHIC REFERENCES: Goldrosen, M.H., Russo, A.J., Howell, J.H., Leveson, S.H., Moore, M.C., Holyoke, E.D., and Douglass, H.O. Jr. Micro-Leukocyte Adherence Inhibition Evaluation as an Immunodiagnostic Test for Pancreatic Cancer. Cancer Res. 39 (February 1979).

70. EVALUATION OF A MICRO-LEUKOCYTE ADHERENCE INHIBITION ASSAY AS AN IMMUNODIAGNOSTIC TEST FOR GASTROINTESTINAL CANCER

Moore, M. C., Goldrosen, M. H., Holyoke, E. D., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *3495 Bailey Ave., Buffalo, New York,* 14215, United States of America

The primary objective of this proposal is to evaluate the potential utility of the leukocyte adherence inhibition assay as a specific immunodiagnostic test for gastrointestinal cancer. This assay will be applied to new patients who are referred to the Gastrointestinal Outpatient Clinic at the Veterans Administration Medical Center, Buffalo, New York. Isolated leukocytes of coded specimens will be evaluated in the micro-LAI assay against pretested biologically active membrane antigen preparations of colon, gastric and pancreatic tumors. Correlation between test results and a patient's clinical status will be performed to determine if this assay is a reproducible, practical and sensitive test for specific forms of gastrointestinal cancer.

To date, 57 patients have been evaluated in this study. From a population of 57 patients, 53 coded specimens were evaluated against a colonic tumor extract, 57 coded specimens were evaluated against the pancreas tumor extract and 40 coded specimens were evaluated against the gastric tumor extract. One coded specimen reacted to the colonic tumor extract while two coded specimens reacted to the gastric tumor extract. The code will be broken once an evaluation of 100 patients has been completed.

71. CHARACTERIZATION OF LAI-DEFINED PANCREAS TUMOR ANTIGENS

Howell, J. H., Goldrosen, M. H., Douglass, H. O., Roswell Park Memorial Inst., Dept. of Surgical Oncology, *666 Elm St., Buffalo, New York,* 14263, United States of America

Patients with pancreatic adenocarcinoma have an extremely high mortality rate. Curative surgery would be more common if early differential diagnosis were feasible. Our group has demonstrated that the micro-leukocyte adherence inhibition assay (micro-LAI) can successfully and specifically detect the presence of pancreatic cancer. In our continuing study to determine the sensitivity of the assay for detection of early cancer, we require a stable, standardized source of pancreas tumor antigen. This will be accomplished by propagating several established low-passage pancreatic adenocarcinoma cell lines in athymic (nude) mice. A membrane extract of each of the lines will be analyzed by micro-LAI and the most consistently reactive tumor line will be grown periodically in large quantity and stable soluble antigen will be prepared for routine use in the assay. Malignant effusion fluid and patients' sera will be biochemically fractionated and selected fractions will be analyzed for reactivity in the LAI assay. Xenogeneic antisera will be prepared against the purified antigen preparations and they will be immunochemically and biochemically compared by serological assays and by 2-dimensional isoelectric-focusing electrophoresis. Radio-iodinated, purified antigen will be prepared and a radioimmunoassay (RIA) will be developed using the most avid xenogeneic antitumor antibodies. Preliminary RIA screening of selected sera from our serum bank will be carried out in a blind fashion. A portion of the pancreas cancer specific antibodies will be labeled with iodine-131 and assayed to determine their suitability for use in external computerized photoscanning for tumor localization. This project will significantly improve the micro-LAI assay and the serological and biochemical data obtained will complement the clinical results.

72. MARKER PEPTIDE AND HORMONE PRODUCTION BY ENDOCRINE AND NON-ENDOCRINE TUMORS

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OBJECTIVE: To study the natural history of tumors of the diffuse endocrine system (apudomas) in order to facilitate early diagnosis and (successful) treatment.

APPROACH: Material from endocrine tumors, human and experimental, is subjected to radioimmunoassay, and to cytochemical and immunocytochemical examinations. Antibodies to a wide spectrum of endocrine peptides are applied and the results are correlated, in the case of human tumors, 1) with clinical symptoms and 2) with serum hormone levels.

PROGRESS: An increasingly large proportion of apudomas are found to be producing more than one (hormonal) peptide. In particular, pancreatic polypeptide (PP) has been established as an important marker for pancreatic tumors. Early diagnosis, especially in cases with high circulating levels of VIP, has enabled us to show that micronodular hyperplasia precedes tumor formation. ACTH-secreting apudomas (pituitary and ectopic) have been shown to contain opioid peptides (endorphins) and these may account for unexplained mental effects in Cushing's syndrome.

73. VASOACTIVE INTESTINAL AND LUNG POLYPEPTIDES - TUMOR

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This proposal deals with the relationship of three newly identified polypeptides, vasoactive intestinal peptide (VIP) and two vasoactive lung peptides, to a number of malignant tumors. Using a sensitive and specific radioimmunoassay (RIA), VIP has been shown to occur normally in the gastrointestinal and nervous systems, and in elevated concentrations in these tumors: pancreatic (islet-cell) adenomas, pheochromocytoma, neuroblastoma, medullary thyroid carcinoma, and bronchogenic carcinoma. The clinical syndrome in common among these tumors was that of watery diarrhea (pancreatic cholera), accompanied in some instances by hyperglycemia, hypercalcemia, hypokalemia and episodic flushing. One vasoactive lung peptide, extractable from normal lung, is related to VIP, cross-reacting with it in the RIA. The other vasoactive lung peptide is spasmogenic and does not cross-react with VIP. Determination of the prevalence of secretion of these peptides in the presence of malignant disease may provide useful clues to the early diagnosis, better management and, possibly also, the pathogenesis of these lesions.

BIBLIOGRAPHIC REFERENCES: Frandsen, E.K., Krishna, G.A., and Said, S.I. Vasoactive intestinal polypeptide promotes cyclic adenosine 3',5'-monophosphate accumulation in guinea pig trachea. Brit. J. Pharmacol. 62:367-369, 1978. Said, S.I. and Zfass, A.M. Gastrointestinal Hormones. Disease-A-Month, 24:1-40, 1978.

74. CARCINOEMBRYONIC ANTIGEN STUDIES

Bagshawe, K. D., Charing Cross Hospital, Dept. of Medical Oncology, *Fulham Palace Rd., London W6 8RF, England, United Kingdom*

OBJECTIVE: To assess the clinical usefulness of carcinoembryonic antigen (1) as a diagnostic aid in patients suspected of having a malignancy and (2) as a means of monitoring patients successfully treated for malignancy.

APPROACH: CEA is being investigated as a diagnostic aid in patients presenting with haematuria and suspected pancreatic disease. The usual diagnostic procedures are carried out and also a plasma specimen, for CEA determination, is taken. CEA is being investigated as an indicator of recurrent carcinoma in patients treated for bladder cancer and colorectal cancer. At each follow-up examination a plasma (and for bladder cancer patients urine) sample is taken for CEA determination. The results are being analyzed.

75. IMMUNOLOGICAL DIAGNOSIS, PROGNOSIS, AND TREATMENT MONITORING OF PATIENTS WITH BENIGN AND MALIGNANT DIGESTIVE TRACT DISEASES

Zamcheck, N., Loewenstein, M. S., Rau, P., Kupchik, H. Z., Mallory Inst. of Pathology Foundation, Gastrointestinal Research Laboratory, *818 Harrison Ave., Boston, Massachusetts,* 02118, United States of America

Measurement of pancreatic juice CEA activity in conjunction with plasma assay levels may help in diagnosing pancreatic cancer and in distinguishing it from pancreatitis. However it is of limited clinical application. Furthermore, our findings to date suggest that the liver plays a key role in regulating circulating CEA levels, extracting the antigen from blood and excreting it, in a measurable amount, in the bile. Again, from the clinical point of view, obtaining bile for measurement of CEA is usually

not practical. If measurement of duodenal juice CEA reflects biliary output, then it is potentially useful. Our preliminary studies give evidence that direct measurement of duodenal juice CEA activity may be of practical use in detecting increased CEA production by primary and metastatic cancers and excretion into the bile and/or pancreatic juice.

The purpose of this study is 1) to assess the practicality of obtaining duodenal aspirates for CEA analysis by employing a new technique for duodenal intubation, 2) to increase the potential usefulness of combining measurement of plasma levels and duodenal output for the early diagnosis of digestive tract malignancy, 3) to asses the usefulness of post-operative and preoperative duodenal juice CEA levels in patients undergoing resection of colorectal cancer, as an index of the completeness of surgical resection, 4) to determine whether increases in duodenal CEA outputs occur prior to elevations in circulating levels, and 5) if so, whether measurement of sequential duodenal CEA outputs in patients with resected colorectal cancers will detect early recurrence, permitting earlier second-look surgery or initiation of changes in treatment.

76. TUMOR ANTIGENS IN PANCREATIC CANCER

Chu, T. M., Douglass, H. O., Lee, C. L., Shimano, T., Loor, R., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

The objective of this proposal is to isolate and purify tumor antigens from pancreatic cancer. The tumor antigens are to be isolated from plasma membrane fraction of the pancreatic tumors, from the extracellular fluid (ascites fluid) and tumor tissues of pancreatic cancer patients. The antigens (free or in complexed form) will be purified by gel filtration, ion-exchange chromatography, affinity chromatography, immunoadsorbent technique, preparative polyacrylamide gel electrophoresis and isoelectric focusing. The chemical, physical and immunological characteristics of the antigens will be studied. Xenobiotic antisera will be raised with the purified antigens and specificity of the antiserum studied. If biochemical and immunologic data indicate that the antigens are specific for or associated with pancreatic cancer, immunodiagnostic procedures will be developed which can be of value in early detection of pancreatic cancer and in monitoring the efficacy of therapy currently available for pancreatic cancer patients. During the past two years of this grant period, a glycoprotein antigen, shown not to be a normal serum component, has been isolated from the ascites fluid of pancreatic cancer patients. A plasma membrane fraction has been prepared from pancreatic tumors which demonstrates a pancreas tumor-associated protease(s) activity. This plasma membrane fraction also contains antigen component(s) which has been used successfully in a leukocyte adherence inhibition assay specifically for diagnosis of pancreas cancer. Pancreatic tumors have been shown to contain perchloric acid soluble antigenic species different from those of colonic CEA. Further, IgM- and IgG-containing immune complexes have been identified in pancreatic cancer patients. The purpose of this renewal proposal is to continue our study of these pancreas cancer-specific or -associated tumor markers and their clinical application.

77. STUDY ON REACTIONS OF TUMOR ANTIGENS WITH THEIR ANTIBODIES

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This is ongoing research with a major objective of developing immunodiagnostic and immunotherapeutic procedures in malignancies. Considerable effort has been devoted to studies on carcinoembryonic antigen (CEA). The diagnosis of tumor based on demonstration of this antigen in feces has been, however, complicated by the appearance of CEA in normal GI mucosa and in food products. Immunization of rats and mice with an antigen analogous to human CEA is being energetically pursued. The appearance of newly discovered pancreas-specific antigen in duodenal contents and feces is being studied as a possible tool for the early diagnosis of pancreatic carcinoma. Formation of antibodies directed against tumor-specific cell-surface antigens (TSCSA) has been studied by means of several sensitive procedures, and diagnostic application of detection of such antibodies is being explored. Studies on genetic control of immune responses to TSCSA have been initiated. Special attention is devoted to antigens shared by tumor cells and normal allogeneic and xenogeneic cells. This includes extensive studies on heterophile antigens, primarily Paul-Bunnell antigen. This antigen was shown to appear not only in the course of infectious mononucleosis, but also in lymphoma and leukemia. The immune response to this antigen appears to be of great importance in the elimination of transformed, aberrant cells. Adsorption by tumor cells of erythrocytes sensitized by IgG antibodies is being explored as an intriguing biological phenomenon and a possible diagnostic procedure. Tumor growth-promoting activity of circulating immune complexes unrelated to the tumor antigens is also being investigated.

78. EXTERNAL DETECTION OF TUMORS BY RADIONUCLIDE LABELLED IMMUNOGLOBULINS

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To date approximately 150 patients (V.A.) have been examined by scanning with antibodies to carcinoembryonic antigen (CEA), alpha-fetal protein (AFP) and human chorionic gonadotropin (HCG) labeled with I-131. Overall sensitivity of the method is about 80% for tumor detection. This figure could be higher except that the resolution limit of available scanning instrumentation is 1-2 cm. Approximately 40 patients with colorectal cancer, 20 with lung cancer, 20 with other digestive tract (pancreas, stomach, esophagus, etc.) cancer have been studied. Plasma levels of circulating antigen do not affect localization by scanning. Surgical specimens have consistently demonstrated tumor to non-tumor ratios of radioactivity to be 2.0-2.5.

The Tc-99m labeling of IgG has been developed to the point of clinical evaluation in lymphoscintigraphic procedures for the detection of nodal metastases. Currently used iodination procedures have been examined as well as the suitability of commercial radioiodide from various suppliers. Amersham and Union Carbide provide products suitable for antibody labeling. The chloramine-T procedure was found to provide the most efficacious labeled proteins in regard to reliability, retention of immunological activity, and suitability for patient administration. Presently studies are underway to evaluate In-III labeled antibodies. Initial results indicate that anti-CEA IgG can be labeled with In-III using DTPA as a chelating agent or bridging intermediate.

79. EARLY DIAGNOSIS OF PANCREATIC CANCER

Geokas, M. C., Largman, C., Brodrick, J. W., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *150 Muir Rd., Martinez, California*, 94553, United States of America

The main objectives of this research project are the isolation, purification, and characterization of an antigen specific for human pancreatic cancer, and the development of a specific radioimmunoassay for its measurement in human serum. Fulfillment of this goal would provide an urgently needed method for the early detection of pancreatic carcinoma. Two possible sources of a pancreatic cancer antigen are fetal pancreas and pancreatic cancer tissue. The goal has been the production of an antisera specific for a fetal pancreas antigen and the testing of this antisera for specificity toward sera of patients with carcinoma of the pancreas. To accomplish this goal, antisera have been raised in rabbits against a stabilized homogenate of fetal pancreatic tissue. Antigens present in normal adult pancreas were absorbed from these antisera by passing the antisera down an affinity column prepared by coupling a stabilized homogenate of adult pancreas to cyanogen bromide-activated agarose. Immunoelectrophoresis using the resulting purified antisera revealed one very strong line versus fetal extract and two additional faint lines versus both fetal and adult extracts. The fetal specific antigen which produced the major line in immunoelectrophoresis migrated with a beta mobility, suggesting that it is distinctly different from alpha-fetal protein.

80. DIAGNOSTIC TEST FOR PANCREATIC CARCINOMA

Klavins, J. V., Long Island Jewish-Hillside Medical Center, *207-05 76th Ave., New Hyde Park, New York*, 11040, United States of America

Human malignant neoplasms and sera, especially from patients with pancreatic carcinoma, will be examined for reactivity

with a tumor specific antiserum developed in our laboratories. Tumor specific antigen in carcinoma of pancreas will be purified applying isoelectric focusing, gel filtration, ion exchange chromatography and gradient centrifugation in an ultracentrifuge.

81. A STUDY OF HUMAN PANCREATIC DUCT ANTIGEN

Gold, D. V., University of Kentucky, School of Medicine, Dept. of Pathology, *Limestone & Euclid, Lexington, Kentucky*, 40506, United States of America

A pancreatic duct antigen will be studied to determine the potential of the antigen as a marker of pancreatic tissue and pancreatic carcinoma in particular. The pancreatic duct antigen will be purified from specimens of normal and neoplastic pancreas and characterized as to amino acid and carbohydrate composition. Antisera will be raised in rabbits and the specific antibody purified by absorption and affinity chromatography. The tissue and tumor specificity of the antisera will be analyzed by immunoperoxidase procedures in a retrospective study of biopsy specimens. A radioimmunoassay will be constructed to compare immunologic relatedness between normal and neoplastic pancreatic duct antigen. Promising antisera will be analyzed for potential use in the immunodiagnosis of pancreatic cancer by quantification of circulating antigen.

82. ORGAN SPECIFIC TUMOR LOCALIZING ANTIBODY

Bale, W. F., Grady, E. D., de los Angeles Contreras, M., Benedetto, W. J., Georgia Inst. of Technology, School of Sciences & Liberal Studies, Dept. of Biology, *Atlanta, Georgia*, 30332, United States of America

The summary for this project is under entry no. 36.

83. CANCER DETECTION PROGRAM

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This is a collaborative project between the Departments of Surgery and Pathology for the early detection of cancer of the pancreas. We will investigate methods of rapid, safe, and easy collection of pancreatic fluid at the time of endoscopy. Three examinations will be performed. In vitro studies on human pancreatic fluid will include 1) cellular studies to detect malignant cells, 2) studies to characterize abnormal enzymes and proteins, 3) immunologic studies of fluid and sera to detect tumor antigens. Two groups of patients will be studied: 1) a group with symptoms pointing to disease of the pancreas, and 2) an asymptomatic group with silent bleeding of the intestinal tract. The principal value of the study is that using these techniques we are testing a remote and inaccessible area for detection of cancer.

BIBLIOGRAPHIC REFERENCES: Goodale, R.L., Condie, R.M., Dressel, T.D., Taylor, T.N., and Gajl-Peczalska, K.: A study of secretory proteins, cytology and tumor site in pancreatic cancer. Annals of Surgery, 189(3):340, 1979. Condie, R.M., Taylor, T.N., Dressel, T.D., and Goodale, R.L.: Intraductal protein changes in pancreatitis and carcinoma of pancreas. Surgical Forum, 30:416, 1979.

2. RADIODIAGNOSTIC METHODS

84. DEVELOPMENT OF EARLY DIAGNOSIS OF CANCER OF THE PANCREAS BY ERCP AND RELATED PROCEDURES

Kasugai, T., Kuno, N., Oguri, T., Matsuura, A., Fujiwara, K., Kurimoto, K., Aichi Cancer Center Research Inst., Dept. of Internal Medicine, *81 1159 Kanokoden Tashiro-cho, Chikusa-ku, Nagoya 464, Aichi, Japan*

OBJECTIVE: Purpose of this study is to develop early diagnosis of cancer of the pancreas by ERCP and related procedures.

APPROACH: (a) Comparative study between pancreatogram and its histology in postmortem pancreatograms. (b) Analysis and interpretation of pancreatograms of small tumors in postmortem pancreatography. (c) Improvement and development of techniques in ERCP for detecting small malignant lesions in the pancreas; direct magnification during ERCP. (d) Study of cytology and biochemical analysis of pure pancreatic juice collected by cannulation. (e) Development and clinical use of screening methods for pancreatic cancer; assays of RNase, CEA and amylase in serum and pure pancreatic juice, and evaluation of combined screening of these tests.

PROGRESS: The branches and fine pancreatic ducts when oparified with contrast material can be studied more precisely after direct fourfold magnification during ERCP than by routine ERCP. Patients with pancreatic cancer showed significantly higher serum RNase activity than patients with chronic pancreatitis or gastric cancer and healthy subjects.

85. LYMPHOGRAPHY IN ONCOLOGIC PATIENTS

Dunnick, N. R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, Clinical Center, Dept. of Diagnostic Radiology, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

OBJECTIVES: To evaluate the role of lymphography in comparison with other diagnostic modalities such as ultrasound and computer tomography in the staging and follow-up of patients with appropriate malignancies.

METHODS EMPLOYED: Bipedal lymphography is routinely performed on patients with a variety of malignancies, most specifically malignant lymphomas, testicular tumors, carcinoma of the prostate, carcinoma of the ovary, and Mycosis fungoides. Follow-up radiographs are performed at periodic intervals and an evaluation of the opacified retroperitoneal lymph nodes is made to assess disease progression.

MAJOR FINDINGS: Bipedal lymphograms performed on a series of 28 patients with carcinoma of the pancreas demonstrated extrapancreatic abnormalities in 4 patients. Indication of extrapancreatic disease may render these patients inoperable.

A method for delivering intralymphatic contrast material to patients who have undergone previous amputations making the usual dorsal pedal lymphatic route impossible was described.

Lymphography has been useful as one of several modalities in following patients with carcinoma of the prostate. It is limited in part by the relatively poor filling of retroperitoneal lymph nodes in older patients. Bipedal lymphography has thus far been quite useful in patients with testicular carcinoma, ovarian carcinoma, and malignant lymphomas. The better detail provided by lymphography is helpful in small sites of metastatic disease. Extranodal disease is more easily detected by computer tomography. Bulky disease can usually be readily identified by either method.

86. DIAGNOSIS OF BILIARY TRACT CANCER USING FINE-NEEDLE TRANSCUTANEOUS CHOLANGIOGRAPHY

Aires Correia, R., De Paula, P., Pessoa, J. B., Fernandez Feijo, S. G., Universidade Federal do Ceara, Hospital das Clinicas, Dept. of Gastroenterologia, *Rua Cap. Francisco Pedro s/n, Porangabussu, Fortaleza 60000, Ceara, Brazil*

OBJECTIVE: To evaluate the cholangiographic methodology using fine-needle, as described by Okuda of the University in Chiba ('Chiba Method') in the differential diagnosis of jaundice. Emphasis is placed on obstructive jaundice involving cancer of the pancreas or biliary tract.

APPROACH: Patients are clinically screened; biochemical parameters such as determination of enzymatic activity of transferases (transaminases), alkaline phosphatase, gammaglutamil transferase, bilirubin, prothombin time, and platelet count are studied. The cholangiographic method used is that described by Okuda.

PROGRESS: We have studied around 70 cases and are expecting a total of 120 patients to be included in the study. (Translated)

87. COMPUTED TOMOGRAPHY IN EVALUATION OF ENDOCRINE PANCREATIC TUMORS, PANCREATIC AND KIDNEY CARCINOMA (ABBREV)

Hemmingsson, A., University Hospital, Dept. of Diagnostic Radiology, *S75014 Uppsala 14, Sweden*

OBJECTIVE: Evaluation of CT, gray scale ultrasonography, scintigraphy and conventional roentgenologic methods will be made in diagnosis, follow-up and spread of endocrine pancreatic tumors, pancreatic carcinoma and kidney carcinoma. Image enhancement with frequency filtration in computed tomography will also be investigated.

APPROACH: Phantom and clinical examination of liver, pancreas and kidney tumors.

88. SYNTHESIS OF NEW 75SE ORGAN SPECIFIC IMAGING AGENTS

Davis, M. A., Hanson, R. N., Northeastern University, School of Pharmacy & Allied Health Professions, Dept. of Medicinal Chemistry, *360 Huntington Ave., Boston, Massachusetts*, 02115, United States of America

This project is concerned with the synthesis and biologic evaluation of selenium containing analogs of a) aromatic amino acids as imaging agents for the detection and differential diagnosis of carcinoma of the pancreas, b) inhibitors of adrenocorticosteroid biosynthesis for the analysis of adrenal cortex pathology, c) levamisole, and immunopotentiating agent, for the analysis of the immune response in cancer patients, d) estradiol for the detection and diagnosis of breast cancer, and e) CNS active drugs for the detection of brain neuropathy. The research goals for this year include evaluating selenium containing analogs of phenylalanine and tryptophan, metyrapone, estradiol and guanosine. These compounds will be administered to rats to determine their pharmacokinetics, biologic distribution, toxicity and ultimate fate. Selenium levels in the tissues will be determined by neutron activation analyses. Those agents that demonstrate in vivo stability and promising target-to-nontarget-organ ratios will be labeled with 75Se and reevaluated using the gamma well counter to determine tissue distribution.

BIBLIOGRAPHIC REFERENCES: P.M. Jacobs and M.A. Davis, Novel synthesis of 2-selenienylalanine. J. Org. Chem. 44, 178-179 (1979). R.N. Hanson and M.A. Davis, Potential adrenal imaging agents. Synthesis and biodistribution of 1,2,3-selenodiazoles. J. Labelled Comp. Radio-pharm. 16, 31-32 (1979).

89. IMAGING IN DETECTION OF EARLY PANCREATIC CANCER

Moossa, A. R., University of Chicago, Pritzker School of Medicine, Dept. of Surgery, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

OBJECTIVES: To establish methods for early detection of pancreatic cancer. To design and be capable of carrying out an extensive and definitive study to improve and evaluate imaging capabilities in the detection of early pancreatic cancer by having available advanced imaging equipment and capability in areas such as ultrasound, computerized axial tomography, etc.; having clinical facilities available to adequately test the efficacy of these modalities; carrying out adequate pathology review, in addition to which pathology slides, blocks, and pathological material will be made available for consultative review; and determining the number of patients to be entered into this study in order to allow for adequate statistical comparisons to be made.

90. EVALUATION OF VALINE-11C AS A PANCREATIC SCANNING AGENT

Laughlin, J. S., Sloan Kettering Inst. for Cancer Research, Biophysics Laboratory, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

91. PANCREATIC TUMOR-DELINEATING RADIOPHARMACEUTICALS

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This is part of a broader project. A summary of this subproject is not available.

3. BIOCHEMICAL AND OTHER DIAGNOSTIC METHODS

92. EARLY DIAGNOSIS OF PANCREATIC CANCER

Geokas, M. C., DelMar, E. G., Largman, C., Brodrick, J. W., University of California, Davis Campus, School of Medicine, Dept. of Internal Medicine, *Davis, California*, 95616, United States of America

The main goal of this research is to determine whether a protein(s) specific for pancreatic carcinoma is present in serum samples obtained from patients with this disease. Previous attempts to detect such a protein in this laboratory by immunological techniques, including production of cancer specific antisera through the use of fetal pancreas extract of pancreatic cancer tissue, have been unsuccessful. We have therefore turned our attention to the detection of a protein specific for pancreatic cancer in patient sera by the two-dimensional gel electrophoresis procedure developed by O'Farrell (J. Biol. Chem. 250, 4007, 1975). Several methods for enhancing the sensitivity and resolving power of this technique for the detection of minor proteins in serum or plasma are currently being evaluated, including selective removal of albumin, a sensitive silver staining procedure, and detection of proteins by autoradiography after labeling by reductive methylation of lysine residues with 14C-formaldehyde. It is expected that the optimized method will be capable of detecting protein spots at an abundance of 10 to the minus 2nd power to 10 to the minus 3rd power percent of total protein. O'Farrell has previously demonstrated that two-dimensional gel electrophoresis can resolve 1100 distinct protein spots in a bacterial cell extract. The technique will be applied to the screening of sera from patients with pancreatic cancer and normal controls in an attempt to detect qualitative changes in the protein pattern that are specific for pancreatic cancer.

The need for early diagnosis of carcinoma of the pancreas is great and we believe that the accomplishment of the goals of this research might eventually lead to a significant breakthrough in improving resectability and survival rate.

93. DIAGNOSIS AND TREATMENT OF PANCREATIC CANCER

Heisler, S., Guderley, H., Universite Laval, School of Medicine, Dept. of Pharmacology, *Ste. Foy, Quebec*, G1K 7P4, Canada

OBJECTIVES: 1. To identify a pancreatic tumor specific marker(s) in human biological fluids which may have potential usefulness in the early diagnosis of pancreatic cancer. 2. To enhance the uptake of currently used anti-neoplastic agents by pancreatic tumors.

APPROACH: 1. Samples of normal and cancerous (diagnosed and undiagnosed) human pancreas will be obtained at surgery or early post-mortem and the cells dispersed by enzymatic digestion. Cells will be superfused and stimulated by secretagogues; the secreted product will be collected and separated by isoelectrofocusing and gel electrophoresis. Secretory profiles of normal and cancerous tissues will be compared in order to ascertain whether quantitative and qualitative differences exist which are unique to pancreatic cancer. 2. A variety of radioactive anti-neoplastic agents will be encapsulated in phospholipid vesicles (liposomes) capable of opening at temperatures slightly above the physiological. The liposomes will be pulsed over superfused human pancreatic acinar cells and the uptake of drug determined as a function of local hyperthermia.

If in the above studies it is not feasible to use human material, the investigation will be pursued using a transplantable pancreatic carcinoma of the rat.

94. EXOCRINE PANCREATIC PROTEINS IN PANCREATIC CANCER

Scheele, G. A., Franklin, J., Rockefeller University, Lab. of Cell Biology, *66th & York Ave., New York, New York*, 10021, United States of America

Two-dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis will be used to characterize proteins contained in pancreatic cancer. Unique proteins will be identified using reductive methylation with H14CHO prior to separation on two-dimensional gels and analysis by fluorography. Proteins will be analyzed for attached carbohydrate of either the complex saccharide or core saccharide type for specific radioactive-labeling techniques. Immunofluorescent localization studies will be carried out to determine the site of origin of unique (glyco) proteins. If antigenic proteins are localized to pancreatic adenocarcinomatous tissue, a radioimmunoassay will be developed using cell hybridization and cloning techniques to provide the required antibodies.

The two-dimensional gel technique will also be used to analyze phenotypic changes among secretory proteins in two animal models of pancreatic adenoma and adenocarcinoma.

95. PANCREATIC DUCTAL VERSUS DUODENAL SECRETIONS

White, T. T., Allan, B. J., University of Washington, School of Medicine, Dept. of Surgery, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The authors are attempting to find tumor markers in pancreatic secretions obtained from human beings at surgery and by ERCP, then to separate the proteins by isoelectric focusing and, finally, analyze the protein patterns using a densitometer which has been coupled with a small computer. The computer then averages and determines statistically the gravities of proteins in each peak, and compares normal secretions from those of patients with cancer and chronic pancreatitis.

BIBLIOGRAPHIC REFERENCES: White, T.T., Slavotinek, A.H.: Results of surgical treatment of chronic pancreatitis. Report of 142 cases. Ann. Surg. 189:217-224, 1979. Tatarchuk, T.W., White, T.T.: A new instrument for inserting a U-tube. Am. J. Surg. 137:425-426, 1979.

96. HUMAN PANCREATIC RIBONUCLEASE AND CANCER

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Human pancreatic ribonuclease has been purified from tissue obtained at autopsy. The enzyme will be characterized in comparison with the well-studied bovine pancreatic RNase, with particular attention to enzyme mechanism and specificity, physical properties, and immunological relatedness. Antibodies directed against the human pancreatic enzyme will be used to quantitate cross-reacting protein in extracts of other human tissues, and to compare the structrue of the enzyme to pancreatic ribonucleases of other organisms. A radioimmunoassay procedure will be used to measure circulating levels of pancreatic RNase in the serum of individuals with pancreatic cancer and related diseases. It is hoped that it will then be possible to resolve the dispute over the value of ribonuclease assays in the detection of pancreatic cancer, and perhaps to develop a practical and useful technique for the early detection of pancreatic carcinoma.

97. RIBONUCLEASES OF HUMAN SERUM AND URINE

Cranston, J. W., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Biological Markers Program, *P.O. Box B, Frederick, Maryland,* 21701, United States of America

The objective of this research project is to evaluate human RNases as useful biological markers of malignant disease with particular emphasis on carcinoma of the pancreas. The value of the RNases in this regard is presently the subject of intense controversy.

Using urine as the source, the initial approach to this problem was to purify and characterize those RNases present in normal humans. These RNases could then be employed in comparison studies with the enzymes present in the urine and sera of patients with malignant and appropriate non-malignant diseases. Methodology employed in these comparison studies includes (1) general biochemical parameters such as molecular weights, amino acid and carbohydrate composition, electrofocusing profiles, amino acid sequences, etc., and (2) the use of antibody directed against the normal RNases to look for possible antigenic differences between RNases from normal versus diseased individuals. A final, clinical approach to the overall problem will include the measurements of serum poly(C)-specific RNase activity present in various samples, with the specific objective of evaluating this particular RNase activity as a biological marker for pancreatic carcinoma. A poly(C) hydrolysis assay, i.e. the catalytic method, as well as a radioimmunoassay, which employs antibody directed against normal urinary poly(C)-specific RNase, will be used in this approach.

Presently, purification and extensive characterization of the only two detectable RNases in normal human urine has been achieved (Cranston et al. (1980) Biochim. Biophys. Acta, in press). A major finding was that a poly(C)-specific RNase, called RNase C, was shown to be a sialylated glycoprotein with marked amino acid sequence homology with all known pancreatic RNases. Preliminary evidence obtained with antibody directed against this enzyme supports the conclusion that the poly(C)-specific RNase present in the sera of all humans thus far tested is antigenically identical to the purified, urinary RNase C.

98. A DETAILED IN VITRO AND IN VIVO BIOCHEMICAL AND IMMUNOLOGICAL STUDY OF HUMAN PANCREATIC EXOCRINE ADENOCARCINOMA

HermonTaylor, J., Grant, A. G., University of London, St. George's Hospital Medical School, Dept. of Surgery, *Cranmer Terrace, London SW17 0RE, England, United Kingdom*

OBJECTIVES: 1) To develop methods to improve the diagnosis of human pancreatic exocrine cancer. 2) To obtain more information about the biological nature of the tumor cells.

APPROACH: a) To study the carbohydrate components of cultured human pancreatic cancer cells expressed on the cell surface. To isolate, purify and identify specific plasma membrane bound macromolecular components and to characterize these chemically and immunologically. b) To develop reagents and cytological assays for the specific recognition of cell surface components. c) To study the behavior of pancreatic exocrine cancer as mouse xenografts.

99. DETECTION OF EARLY PANCREATIC CANCER - ROLE OF RIBONUCLEASE, PANCREATIC ONCOFETAL ANTIGEN AND OTHER TUMOR-ASSOCIATED ANTIGENS (ABBREV)

Tytgat, G. N., Teunen, A., Huibregtse, K., de Vet, B., Hoek, F., Hoitsma, H. F., Universiteit van Amsterdam, Dept. of Medicine, *Spui 21, Amsterdam, Netherlands*

OBJECTIVE: Evaluation of various new methods for detection of pancreatic cancer (screening for pancreatic function abnormalities with PABA test and Lundh test; determination of ribonuclease, pancreatic oncofetal antigen, CEA and lactoferrin, in serum and in pure pancreatic juice; analysis of endoscopic retrograde pancreatographic findings in various diseases of the pancreas; correlation of the findings with the final state of patients with pancreatic cancer).

APPROACH: a) Determination of ribonuclease, pancreatic oncofetal antigen and other tumor-associated antigens in the serum of 100 patients with various abdominal malignant and nonmalignant conditions and of 100 normal age- and sex-matched control subjects. b) Detailed study of 100 patients, referred for a suspicion of possible pancreatic malignancy by 1) analysis of pancreatic functions using the PABA test, Lundh test, secretin pancreozymin test, fecal fat excretion rate, etc.; 2) determination of ribonuclease, pancreatic oncofetal antigen, CEA, and lactoferrin in serum and pure pancreatic juice; 3) critical analysis of radiological findings on the pancreatic ductal system obtained by endoscopic retrograde cholangiopancreatography; 4) cytological examination of pure pancreatic juice for exfoliating malignant cells; and 5) correlation of all the above findings with the final diagnosis and condition of the patients with and without pancreatic cancer.

100. ZOLLINGER-ELLISON SYNDROME STUDIES

Passaro, E. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *Wilshire & Sawtelle Blvds., Room 209, Los Angeles, California,* 90073, United States of America

PURPOSE: To measure a-HCG (alpha human chorionic gonadotropin) levels in gastrinoma patients and patients with duodenal ulcer disease. Also to evaluate Z-E (gastrinoma) patients, under both stimulated and basal conditions, to determine whether or not prolactin levels can be used as an indicator of the malignancy of these adenomas.

A total of 36 ZES patients have thus far been evaluated with serum prolactin determinations. Eight of these have been found to have elevated levels and seven are thought to have pituitary prolactomas. Tissue confirmation has been made in 2 and the remaining 5 have suggestive x-ray and/or thyrotropin releasing hormone stimulation tests. These patients are essentially asymptomatic and are being followed with serial prolactin measurements and close clinical observation. These patients, and our other ZES patients, will continue to be followed.

101. IN VITRO ASSAY FOR INCREASED RISK FOR PANCREATIC CANCER

Danes, B. S., Cornell University, Medical Center, Cornell Medical College, Dept. of Medicine, *1300 York Ave., New York, New York,* 10021, United States of America

In vitro research on the identification of increased risk for pancreatic cancer within families with pancreatic cancer with

and without other solid tumors was based on the hypothesis that a cell considered normal by all criteria in a clinically normal individual, when grown in culture, would demonstrate such a mutant cancer-prone genotype. This hypothesis was based on in vitro research on the inborn errors of metabolism and the heritable colon cancer syndromes.

Dermal (fibroblast and epithelial) cultures were established from affected members, family members considered to be at increased risk and family members by marriage who did not have a family history of solid tumors as controls.

Increased in vitro tetraploidy has been observed in members at increased risk for pancreatic cancer in association with other solid tumors (offspring of affected persons). On the basis of this finding, increased in vitro tetraploidy may be useful in detecting risk for pancreatic cancer in families with heritable cancer syndromes involving more than 1 organ site. A cancer-prone gene expressed as solid tumors including pancreas in vivo may be detected in vitro by increased tetraploidy. Further research should demonstrate if increased in vitro tetraploidy identifies members at increased risk in families with pancreatic cancer.

102. C-REACTIVE PEPTIDE IN DIAGNOSIS OF INSULINOMA OF PANCREAS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

103. DIAGNOSTIC METHODS IN PANCREATIC CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

B. PATHOPHYSIOLOGY

104. SIGNIFICANCE OF ALTERED TSH SECRETION

Ridgway, E. C., Klibanski, A. C., Kieffer, J. D., Chin, W. W., Cooper, D. S., Maloof, F., Massachusetts General Hospital, Dept. of Medicine, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

Patients with diseases of the thyroid or pituitary gland have abnormalities in the biosynthesis, secretion, and regulation of TSH and its subunits. The proposed studies in this application will investigate the molecular events in the biosynthesis of TSH and its subunits.

TSH is one of a family of glycoprotein hormones that consists of two non-covalently linked, dissimilar subunits, designated alpha and beta. We propose to investigate the cellular events that take place in the biosynthesis of TSH. We wish to determine how these processes are regulated, how they may be interdependent, and how they may be involved in intracellular transport, packaging, and secretion of hormone. The isolation of mRNA coding for the TSH subunits and the production of cDNA to mRNA will allow study of the translation and transcriptional process. With this background, detailed studies and substantive information will be derived on the regulation of those mechanisms responsible to TSH and subunit biosynthesis. Our initial studies on regulation will be performed on normal bovine anterior pituitaries placed in monolayer culture, and then compared with similar studies using the neoplastic mouse thyrotropic tumor.

Our human studis will determine and quantitate the metabolic consequences of varying degrees of disordered thyroid function particularly as they relate to cardiovascular and pituitary function. In addition, we will expand our investigation of pituitary tumors to assess the efficacy of TSH and subunit measurements for the diagnosis and care of these patients. Unbalanced or discordant alpha and TSH-beta subunits will be carefully quantitated to determine differences in the biosynthesis of glycoprotein subunit in normal and neoplastic tissues.

BIBLIOGRAPHIC REFERENCES: Cooper, D.S., Ridgway, E.C., Kliman, B., Kjellberg, R.N., and Maloof, F.: Metabolic clearance and production rates of prolactin. J. Clin. Invest. 64: 1669-1680, 1979. Nathan, D.M., Daniels, G.H., and Ridgway, E.C.: Gastrinoma and phaeochromocytoma: Is there a mixed multiple endocrine adenoma syndrome? Acta Endocrinol. 93: 91-93, 1980.

105. IMMUNOCHEMICAL STUDIES OF SECRETIN

Kolts, B. E., State University System of Florida, University of Florida, School of Medicine, Dept. of Medicine, *1600 Archer Rd., Box J-266, Gainesville, Florida*, 32610, United States of America

The overall objective of this proposal is to obtain important information concerning the nature, control and effects of the gastrointestinal hormone, secretin. This hormone is selected for study for several reasons. Recognized as a mediator of gastrointestinal alkaline secretions, secretin has been suggested to play an etiologic role in the symptomatology of WDHA syndrome associated with an endocrine tumor of the GI tract. It has also been suggested as an inhibitory modulator of gastric acid secretion. Until recently physiological concepts of these actions of secretin and others were based on studies such as bioassays utilizing indirect measurement of limited sensitivity and specificity. This request proposes to study secretin peptides contained in intestinal mucosa and released into the circulation by intraduodenal acidification utilizing chromatographic and specific, sensitive radioimmunoassay techniques. The secretin content of gastric and small intestinal mucosae and sera obtained during fasting and under stimulated conditions will be determined utilizing healthy human and canine subjects. Values obtained will be compared and contrasted with those from studies of conditions associated with gastric acid hypersecretion (Zollinger-Ellison syndrome and massive small bowel resection) and hyposecretion (histamine-fast achlorhydria). In order to evaluate the pathophysiologic role of secretin in the WDHA syndrome, sera and metastatic tissues will also be assayed for secretin content. Immunochemical heterogeneity of secretin from the mucosa and circulation will be characterized by gel filtration chromatography. Activities to improve the secretin immunoassay will be continued; specific plans for improvement in antibody affinity and further documentation of antibody specificity will be prepared, and improvement of radiosecretin purity with increased specific activity will be accomplished.

BIBLIOGRAPHIC REFERENCES: Kolts, B.E., Sekine, T., McDonald, A.P., Snyder, S.T., and Woodward, E.R. Absence of a secretin response to ethanol ingestion in human and canine subjects. Clinical Research 25:313A, 1977. Brady, P.E., and Kolts, B.E. The effect of cigarette smoking on immunoreactive gastrin and secretin in healthy human volunteers and patients with duodenal ulcers. Clinical Research 25:308 A, 1977.

106. PANCREATIC SECRETORY PROTEINS IN CANCER OF THE PANCREAS

Rinderknecht, H., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

The aim of the proposed work is to analyze pancreatic secretions of patients suspected of having cancer of the pancreas or with a positive diagnosis of cancer of the pancreas and to compare them with secretory profiles obtained from healthy volunteers in the hope of detecting qualitative or quantitative abnormalities that might help in the early diagnosis of this disease. These studies will be accompanied by a similar investigation in hamsters during induction of pancreatic neoplasms with nitrosamines. Pancreatic tissue and fluid of groups of treated and untreated animals will be analyzed at regular intervals for changes in various parameters which in human patients have indicated the presence of pancreatic disease. Thus, ratios of trypsinogen variants, trypsin inhibitor, chymotrypsinogen and a number of lysosomal enzymes will be determined. Highly sensitive methods developed previously for investigation of human pancreatic fluid will be adapted for pancreatic tissue and fluid from hamsters. Data obtained from these assays will be correlated with concurrent histological studies in order to explore the possibility that changes in secretory proteins may precede recognizable histological abnormalities characteristic of tumor cells. Such changes or combination of changes might serve as sensitive markers for present or incipient pancreatic pathology.

BIBLIOGRAPHIC REFERENCES: Trypsinogen Variants in Pancreatic Juice of Healthy Volunteers, Chronic Alcoholics and Patients with Pancreatitis and Cancer of the Pancreas. H. Rinderknecht, I.G. Renner and C. Carmack. Gut 20:886-

891 (1979). Trypsinogen Variants in Pancreatic Juice of Healthy Volunteers, Chronic Alcoholics and Patients with Pancreatitis and Cancer of the Pancreas. H. Rinderknecht, I.G. Renner and C. Carmack. Medical Digest (Gastroenterology Digest) in press (1980).

107. ENDOCRINE TUMORS OF THE PANCREAS

Yamaguchi, K., Abe, K., Oka, Y., Ministry of Health & Welfare, Endocrinology Div., *Tokyo, Tokyo, Japan*

OBJECTIVES: Clinical features of patients with endocrine tumors of the pancreas are extremely variable, depending on the hormone produced by the tumor. Furthermore, our recent observations indicate that these tumors produce multiple hormones. The project seeks to clarify the relation between the clinical features and the hormone produced by the tumor.

APPROACH: Using radioimmunoassay, plasma levels and tumor contents of various hormones, such as insulin, C-peptide, glucagon, pancreatic polypeptide, somatostatin, VIP, gastrin, calcitonin, secretin, motilin, ACTH, beta-MSH and substance P, are being examined.

BIBLIOGRAPHIC REFERENCES: K. Abe, K. Yamaguchi, I. Adachi and N. Yanaihara: Multiple hormone production in islet-cell tumors. In Proinsulin, Insulin, C-peptide. Edited by S. Baba, T. Kaneko and N. Yanaihara. Excerpta Medica, Amsterdam-Oxford, 1979, pp. 374-379. K. Yamaguchi, K. Abe, S. Miyakawa, S. Ohnami, I. Adachi, Y. Oka, M. Ueda, T. Kameya and N. Yanaihara: Multiple hormone production in endocrine tumors of the pancreas. In Gut Peptides. Edited by A. Miyoshi, Kodansha, Tokyo, 1980, (in press).

108. CANINE CARCINOGENESIS - ESOPHAGEAL AND PANCREATIC

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Carcinoma of the esophagus and carcinoma of the pancreas are among the most lethal of human neoplasms. Efforts to devise successful therapeutic regimens for the primary neoplasm are hampered by lack of an animal model suitable for the study of surgical procedures or radiation therapies appropriate for use in man.

Using carcinogens with proven effect in small animals, we have successfully induced invasive bronchogenic carcinoma in dogs. In this application, we propose to extend this approach to the development of carcinoma of the esophagus and carcinoma of the pancreas in dogs. Achievement of a predictable model of esophageal and pancreatic cancer, in which the lesion is reproducible at pre-selected localized sites, will provide 1) opportunities for studying the transition of normal tissues into pre-neoplastic and neoplastic lesions, 2) a preparation for serial diagnostic studies utilizing methods feasible in man but not possible in the small animals usually employed in carcinogenesis research, and 3) a potential for meaningful therapeutic investigations using this large animal model for esophageal and pancreatic carcinoma.

As the work progresses and neoplastic lesions are produced, collaborative projects conducted in cooperation with other members of the City of Hope Cancer Research Center will be developed. These will include basic immunologic and cytogenetic studies of the evolving tumors, and multimodality therapeutic approaches involving radiation and medical oncology.

109. CHARACTERIZATION OF A PANCREATIC ACINAR CARCINOMA

Gunther, G. R., St. Jude Children's Research Hospital, Dept. of Biochemistry, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The overall objectives of this project are to gain a basic understanding of the mechanism of hormone-mediated discharge in the pancreatic acinar cell, and to establish an experimental model for pancreatic cancer to aid in the study of etiology, diagnosis and treatment of this disease. This is being approached by characterizing the hormone-responsiveness and surface membrane components of a moderately differentiated transplantable rat pancreatic acinar carcinoma (J.K. Reddy and M.S. Rao (1977) Science, 198: 78-80). Specific aims are to (1) Compare the discharge response of normal pancreatic acini to that of tumor cells regarding efficacy and potency of secretagogues, increases in cGMP, changes in intracellular calcium, and the role of calmodulin; (2) compare surface properties in terms of number, affinity and distribution of peptide hormone receptors and antigenic or iodinatable components on the plasma membrane; and (3) adapt the pancreatic carcinoma to in vitro culture in order to study differentiation and morphogenesis. Normal acini and dissociated tumor cells will be prepared using purified collagenase. Secretion stimulated by cerulein, carbamylcholine, and other agents will be measured by release of amylase and pulse-labeled protein. Antisera to tumor cells will be absorbed with normal tissue and used in immunoprecipitation of detergent-solubilized cell extracts coupled with cell iodination, gel electrophoresis and autoradiography. Characterization will be aided by correlation of results from all areas.

110. SYRIAN HAMSTER MODEL OF PANCREATIC CARCINOGENESIS

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In our search for an inbred Syrian hamster which may be more susceptible to BOP pancreas cancer induction than other types of hamsters we shall first determine the most effective dose of BOP in our BIO 15.16 carcinogen-susceptible strain (now under way). As soon as they will be available, animals of the BIO 14.6 inbred strain will be studied because a fine structural pancreatic anomaly (marked distortion of endoplasmic reticulum in exocrine cells and occasional islet cells) has been noted, implying possible metabolic anomalies. The pancreatic response of these animals to BOP will be compared with those of a carcinogen-resistant inbred strain BIO 1.5 and with those of a hybrid bred from two carcinogen-susceptible inbred strains.

111. BILIARY RADIOGRAPHIC CONTRAST MATERIALS

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We propose to study the physiology, biochemistry and pharmacology of compounds that are used or have been proposed for use in the radiographic opacification of the gallbladder and bile ducts in order 1) to provide basic data concerning the mechanism of absorption, uptake and excretion of these compounds that have been used empirically in large quantities for many years, 2) to provide a rational basis for the selection of the best compound and for the most efficient, safe and economical use in clinical practice, 3) to use these data to elucidate the basic mechanisms involved with hepatic biochemistry and physiology, especially as they relate to bilirubin metabolism, 4) to develop an improved, safer and more efficient biliary contrast agent, and 5) to use these data to develop contrast materials for use with computerized tomography for evaluation of the pancreas. The last would extend the usefulness of computerized tomography and allow diagnosis of cancer of the pancreas and other diseases at an earlier stage than ever before possible.

112. CANCER STUDIES WITH NEW RADIOACTIVE SCANNING COMPOUNDS

Laughlin, J. S., Sloan Kettering Inst. for Cancer Research, Biophysics Laboratory, *410 E. 68th St., New York, New York*, 10021, United States of America

The objectives of these studies are to identify and investigate the degree of tumor localization, selective organ localization and metabolic rates of specific biologically significant compounds labeled with short-lived nuclides. These labeled compounds will be evaluated as agents for early detection of cancer, will be used to define chemical and biological events leading to carcinogenic reactions and will be studied in normal and abnormal metabolic circumstances. The radionuclides used in the study are all produced in the cyclotron, have short half-lives which greatly reduce patient exposure and require detection apparatus suitable for high energy radiation. These studies will be evaluated in animals and man with quantitative scanning and imaging systems.

Specific proposed studies in order of priority: 1) Nitrogen-13 Compounds for Tumor and Organ Imaging in Human Cancer Patients; 2) Evaluation of 11C-Amino Acids as Pancreatic Imaging or Tumor Localization Agents; 3) Evaluation of 11C-Thymidine as a Potential Tumor Localizing Agent; 4) In Vivo Disposition of N-13 Labeled Nitrate, Nitrite and Nitroso-

carbaryl; and 5) Localization of Soft Tissue Tumors with 73Se-Selenite.

BIBLIOGRAPHIC REFERENCES: Gelbard, A.S., Benua, R.S., Laughlin, J.S., Rosen, G., Reiman, R.E., and McDonald, J.M. Quantitative scanning of osteogenic sarcoma with nitrogen-13 labeled L-glutamate. J. Nucl. Med. 20:782-784, (1979). Gelbard, A.S., Benua, R.S., McDonald, J.M., Reiman, R.E., Vomero, J.J., and Laughlin, J.S. Organ imaging with 13N-L-glutamate. J. Nucl. Med. 20: 663, (1979).

113. PANCREATIC ISLET CELL TUMORS (HUMAN)

Field, J. B., University of Pittsburgh, School of Medicine, Dept. of Medicine, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

This is part of a broader project. A summary of this subproject is not available.

114. ISLET CELL TUMOR (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

115. GLUCOSE TOLERANCE IN PATIENTS WITH PANCREATIC CARCINOMA

Rubenstein, A. H., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

116. GLUCAGON SECRETION BEFORE AND AFTER GLUCAGONOMA REMOVAL (HUMAN)

Horton, E. S., University of Vermont & State Agricultural College, School of Medicine, Dept. of Medicine, *85 S. Prospect St., Burlington, Vermont*, 05401, United States of America

This is part of a broader project. A summary of this subproject is not available.

117. HORMONE PRODUCING TUMORS OF PANCREAS (HUMAN)

O'Dorisio, T. M., Ohio State University, Columbus Campus, School of Medicine, Dept. of Medicine, *370 W. 9th Ave., Columbus, Ohio*, 43212, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. THERAPY

1. CHEMOTHERAPY

118. CHEMOTHERAPY OF HUMAN PANCREATIC TUMORS GROWN IN NUDE MICE

Duke, D. I., Hellmann, K., Hutchinson, G. E., Pym, B., Imperial Cancer Research Fund, Cancer Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The incidence of adenocarcinoma of the pancreas is steadily increasing. It is difficult to diagnose at a stage when surgery and/or radiotherapy might be successful and chemotherapy has proved on the whole to be clinically ineffective.

In current studies using human pancreatic tumor xenografts in nude mice, a combination of 5-fluorouracil, cyclophosphamide, razoxane and prednisone has been shown to inhibit tumor growth. Singly, none of these drugs had a significant effect but the combination caused total inhibition of growth or even tumor regression without concomitant toxicity. Tests were carried out on established actively growing tumors that had undergone at least a 2-4 fold increase in volume before drug treatment had started. Variations in dose levels and timing of drug administration and the action of this drug combination on other human tumor xenografts is now being examined.

119. CHEMOTHERAPY RESPONSE OF HUMAN SOLID TUMOR XENOGRAFTS

Chu, M. Y., Melvin, J., Brown University, Roger Williams General Hospital, *825 Chalkstone Ave., Box 1883, Providence, Rhode Island*, 02908, United States of America

Previously established human lung carcinoma Lx-1 has been investigated. The existence of tumor cell heterogeneity in human lung carcinoma Lx-1 has been demonstrated by morphology and by differential drug sensitivity of its four subclones isolated in culture. In collaboration with Dr. R. E. Parks, Jr., an effective combination chemotherapy has been established based on the finding that formation of biologically active nucleotides of the adenosine analogs is greatly increased by pretreatment of cells with 2'-deoxycoformycin (dCF). In culture, dCF pretreatment for 15 minutes greatly potentiates 8-azadenosine (8-Aza-Ado) activity against human lung carcinoma Lx-1 and its four subclones with varying degrees of sensitivity. The in vivo studies using ATS-mouse xenografts showed that dCF (0.025 mg/kg/day x 1) one hour pretreatment, followed by 8-Aza-Ado (40 mg/kg/day x 1) significantly reduced the tumor weight to 35% of the untreated control while 8-Aza-Ado alone had no effect. This combination given on days one and three completely inhibited tumor growth with no sign of toxicity as animals gained weight. The combination of dCF and Ara-A against Lx-1 and its four subclones was carried out in culture and in ATS-mouse xenografts.

The in vitro drug sensitivity studies of malignant effusion from a patient with pancreatic tumor showed that after 24 hours of incubation, adriamycin at 10 to the minus 5th power M caused a 60% decrease in cell number when compared to the untreated control. At an equal molar concentration (10 to the minus 5th power M) 5-FU and BCNU decreased the cell number by only 14% and 21% respectively. The patient achieved a partial response with single agent, adriamycin.

120. CALGB 7982 - CHEMOTHERAPY OF ADVANCED PANCREATIC CANCER - A COMPARATIVE PHASE II STUDY OF FAM VS SMF

Nayfield, S. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *1201 Broad Rock Rd., Richmond, Virginia*, 23249, United States of America

Carcinoma of the pancreas usually presents as advanced disease, surgically unresectable and poorly responsive to most chemotherapeutic agents.

PURPOSE: To compare efficacy of combination chemotherapy with 5-fluorouracil-adriamycin-mitomycin C versus streptozotocin-mitomycin C-5-fluorouracil treatment of pancreatic carcinoma.

PLAN: Patients with unresectable pancreatic carcinoma or recurence following surgery are randomized to Regimen I (SMF): streptozotocin 1.0 gm/M2 (i.v.) days 1,8,29,36; mitomycin C 10 mg/M2 (i.v.) day 1; and 5-fluorouracil 600 mg/M2 (i.v.) days 1,8,29,36; or Regimen II (FAM), which substitutes adriamycin 30 mg/M2 (i.v.) days 1,29 for streptozotocin. Drug dose is modified for hematologic or cardiac toxicity and renal or hepatic dysfunction. Therapy is continued until progression of disease or relapse occurs. Information is submitted to CALGB for analysis as a part of their multi-institutional study.

121. PHASE II COMBINATION STUDIES IN PANCREATIC CANCER

Schein, P. S., Woolley, P. V., Smith, F. P., Byrne, P., Widerlite, L., Matthews, M., Anderson, T., Georgetown University, School of Medicine, Dept. of Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

Phase II studies of combination chemotherapy in patients with advanced pancreatic cancer are now being conducted. The first combination of 5-FU, adriamycin, mitomycin-C and chlorozotocin (FAM-Chloro) has been completed.

The second proposal is the study of a combination of 5-FU, adriamycin and cis-diammine-dichloroplatinum.

122. PHASE II STUDY OF CHLOROZOTOCIN

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This is a study designed to test the efficacy and safety of chlorozotocin in patients with advanced cancer. Patients are eligible for treatment with this drug if they have histologically confirmed advanced cancer of the GI tract, pancreas, lung, breast, melanoma or lymphoma. Chlorozotocin is given at a dose of 120 mg/m2 every six weeks. This is part of a larger group study and the results are not available at this time.

123. AAFC IN COMBINATION IN UPPER GI TRACT ADENOCARCINOMA

Alberto, P., Seematter, R., Abele, R., Hopital Cantonal, Dept. of Medicine, *64 Ave. de la Roseraie, 1211 Geneva 4, Switzerland*

OBJECTIVE: To assess the effectiveness and tolerance of AAFC (anhydro-ara-5-fluorocytidine) in combination with 5-fluorouracil in adenocarcinoma of stomach, pancreas, gallbladder and esophagus.

APPROACH: Open non-randomized study for pretreated and non-pretreated patients. AAFC: 600 mg/m2 weekly, 5FU : 400 mg/m2 weekly. Duration 6 weeks or more.

PROGRESS: Ten patients. No preliminary report.

124. CLINICAL ONCOLOGY (MULTIDISCIPLINARY)

Carbone, P. P., University of Wisconsin, Madison Campus, Center for the Health Sciences, Dept. of Human Oncology, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

Projects included in this program focus on the natural history, causation, detection, and experimental treatment of solid tumors, stressing use of chemotherapeutic drugs and modulators of the immune and endocrine systems. Clinical trials for breast and pancreatic tumors; causation, early detection and intravesical treatment of bladder tumors; analysis of bony metastasis and hypercalcemia in breast and prostate cancers; in vitro and clinical immunological effects of levamisole and interferon; and pharmacology and clinical efficacy of platinum-containing coordination compounds and antiestrogens comprise studies under way.

The program depends on interdisciplinary collaboration of laboratory and clinical investigators, biostatisticians, and data management experts devoted to an integrated, interactive effort.

BIBLIOGRAPHIC REFERENCES: Tormey, D.C., and Carbone, P.P. What is the optimum number of agents? Int. J. Radiation Oncology Biol. Phys. 4: 301-303, 1978. Davis, T.E., and Carbone, P.P. Drug treatment of breast cancer. Drugs 16: 441-464, 1978.

125. EXPERIMENTAL CHEMOTHERAPEUTICS OF PANCREATIC CANCER

Chang Wai Ling, B. K., Medical College of Georgia, School of Medicine, Dept. of Medicine, *1459 Gwinnett St., Augusta, Georgia,* 30902, United States of America

Despite the need for improvement in the therapy of pancreatic cancer (non-endocrine), there is very little published information on the handling of chemotherapeutic drugs by the pancreas or by adenocarcinoma of the pancreas. Furthermore, the response to chemotherapy of pancreatic adenocarcinoma has been difficult to evaluate by means of clinical trials, in part because of the frequency of far advanced or non-measurable disease in this disorder. Thus, experimental approaches aimed at corrrecting these deficiencies would appear to be warranted. The study proposed herein would focus on the relationship between the tissue uptake and disposition (including metabolism) of chemotherapeutic agents by the pancreas and pancreatic carcinoma and the antitumor activity of these agents. Two animal tumor models have been chosen as appropriate (because of their correspondence to two types of human pancreatic adenocarcinoma) for the the investigations: a) a ductal adenocarcinoma, passaged in inbred Syrian hamsters (courtesy of Drs. Rao and Scarpelli, Northwestern University), and b) an acinar adenocarcinoma, passaged in Fischer 344 rats (courtesy of Drs. Reddy and Rao, Northwestern University). Initial investigations will be carried out with drugs that have shown some activity in pancreatic cancer -i.e., adriamycin, 5-fluorouracil, and mitomycin C. (Preliminary experiments in my laboratory in normal Fischer 344 rats show a relatively high uptake of adriamycin and long tissue half-life in the pancreas.) Later studies would involve drugs that have not received adequate clinical trial in pancreatic cancer, but that have a fairly broad spectrum of activity - namely, methotrexate, actinomycin D, vincristine and vinblastine. Such studies could be extended to include other drugs, especially those of an investigative nature. The ultimate goal of the project is to provide information that would permit more rational and informed clinical trials and to provide a basis for the understanding of the sensitivity and/or resistance of pancreatic cancer to chemotherapy.

126. PURIFICATION, SYNTHESIS AND POSSIBLE CLINICAL APPLICATION OF PANCREOTONE

Harper, A. A., Hood, A. J., Mushens, J., Smy, J. R., Veitch, R. K., University of Newcastle upon Tyne, School of Medicine, Dept. of Pharmacological Sciences, *6 Kensington Terr., Newcastle upon Tyne NE1 7RU, United Kingdom*

OBJECTIVE: Pancreotone, a polypeptide material in extracts of porcine ileal mucosa, inhibits exocrine pancreatic secretion in cats. Administered subcutaneously to young rats, pancreotone produced a significant atrophy of the pancreas. Pancreatic RNA and protein were reduced, but DNA was unchanged. Dosage was limited by the impurity of the extracts.

The objectives of the research are (a) to purify pancreotone, ascertain its structure and synthesize it; (b) to repeat the observations on pancreatic growth in rats with larger doses of purified material to ascertain whether hypoplasia as well as atrophy can be produced; (c) to establish a radioimmunoassay for pancreotone; and (d) depending on the availability of purified material and the results of (b), to study the effects of pancreotone in carcinoma of the pancreas in man.

APPROACH: Large amounts of crude pancreotone extracts are prepared by Hazleton Laboratories Europe Ltd. These are purified in the Pharmaceutical Division of Imperial Chemical Industries Ltd. (principal collaborators, J.S. Morley and N. Petter). The activity of the crude extracts and the purified fractions is assayed on cats in Newcastle.

PROGRESS: During the first year of the project a partial purification of pancreotone has been achieved. It is hoped that in the second year the confirmatory experiment on the effect of larger amounts of pancreotone on pancreatic growth can be completed.

127. PANCREATIC CARCINOMA IN CONTINUOUS CULTURE

Yunis, A. A., Schultz, D. R., Wu, M., Arimura, G. K., University of Miami, School of Medicine, Dept. of Medicine, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida,* 33152, United States of America

Human pancreatic carcinoma in continuous culture is being used as an experimental model to investigate 3 areas in all of which considerable work has been done in this laboratory: 1. Purification of a tumor-related antigen is underway. This antigen has been identified and appears to be immunologically identical to oncofetal antigen. We plan to develop a radioimmunoassay for this antigen and proceed to do large-scale testing of human sera. The effect of the antibody to the antigen on the growth and tumorigenicity of MIA PaCa-2 in nude mice will also be tested. 2. We have identified two proteolytic activites in cultured MIA PaCa-2, a plasminogen activator and a membrane protease. The latter will be purified and its role in tumorigenicity and tumor invasiveness will be assessed. 3. Extensive screening of chemotherapeutic agents will be performed on the cultured cells. Drugs found to have some effect on growth will be examined in depth for their effects on the cell cycle and various metabolic aspects of the cells.

Particular attention is being given to the potential role of glutamine antagonists as anti-pancreatic cancer agents.

BIBLIOGRAPHIC REFERENCES: Schultz, D.R., and Yunis, A.A.: Tumor Associated Antigen(s) in Human Pancreatic Cancer. J. of the Natl. Cancer Inst. 62: 777, 1979. Allen, L., Meck, R., and Yunis, A.A.: Inhibition of gamma-Glutamyl Transpeptidase from Human Pancreatic Carcinoma Cells by (gamma-S, 5S)-alpha-amino- 3 -chloro-4,5-dihydro- 5 -isoxazoleacetic acid (AT-125; NSC, 163501). Res. Comm. Chem. Path. and Pharm. 27: 175, 1980.

128. CHEMOTHERAPY OF ADVANCED PANCREAS CARCINOMA

Livstone, E. M., Yale University, School of Medicine, Dept. of Medicine, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

129. STREPTOZOCIN FOR INSULIN PRODUCING METASTASES FROM ISLET CELL NEOPLASM

Ensinck, J. W., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

This is part of a broader project. A summary of this subproject is not available.

130. INFUSION OF SOMATOSTATIN FOR GLUCAGON SECRETING TUMOR (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

2. RADIOTHERAPY

131. MICROWAVE-INDUCED HYPERTHERMIA FOR DEEP-SEATED TUMORS

Douple, E. B., Strohbehn, J. W., Walsh, J. E., Bartrum, R. J., Roberts, D. W., Saunders, R. L., Dartmouth College, Dartmouth Medical School, Dept. of Medicine, *P.O. Box 833, Hanover, New Hampshire*, 03755, United States of America

This project proposes to use an invasive microwave irradiation system to achieve local hyperthermia for the treatment of deep-seated cancers. Microwaves in the GHz range are characterized by short energy absorption lengths in living tissue. It is proposed that this characteristic will be exploited and the energy will be delivered directly to the tumor site through transmission lines and antenna structures which have been developed in our laboratory. Antenna probes with diameters less than 1 mm will be employed. Thus, implantation can be performed with minimal disturbance to the surrounding tissue, and many of the problems associated with the delivery of heat to deep-seated tumors will be circumvented.

The objectives of this study are: (1) To further develop an invasive system for heating deep-seated tumors and to adapt the system for percutaneous insertion and surgical implantation so as to produce appropriate hyperthermia in difficult to heat, deep-seated tumors in humans; (2) to predict theoretically, and to measure experimentally, the heat distributions produced by the improved system in tissue phantoms, tumors and normal tissues of animals and humans; (3) to evaluate the therapeutic efficacy of the proposed system by studying the effect of the induced hyperthermia, alone, and in combination with ionizing radiation and chemotherapy on animal tumors, and in pilot clinical studies; and (4) to examine the effect of local hyperthermia on blood flow and the uptake of chemotherapeutic drugs in tumors and in normal tissues.

These tumors will include transplantable mouse mammary adenocarcinoma (MTG-B), chemically induced tumors in the rat, and spontaneous brain tumors in dogs. The effects of the treatment on tumor cell viability will be assessed using the TD50 and tumor latency assays as well as histological evaluation. Tumor growth, TCD50 and host lifespan will also be studied as indicators of therapeutic effectiveness, and normal tissue response will be carefully observed in heated animals. Clinical tumors will include brain tumors and other tumors such as pancreas and prostate cancer.

132. INTRAOPERATIVE RADIATION THERAPY FOR PANCREAS CANCER

Goldson, A. L., Ashayeri, E., Roux, V. J., Cornwell, E. E., Rayford, L. L., Chisholm, R., Howard University, School of Medicine, Dept. of Radiation Therapy, *2400 6th St. N.W., Washington, District of Columbia*, 20001, United States of America

Intraoperative radiotherapy (IOR) of 15 patients with advanced pancreas cancer using 9-15 MeV electron beams of a linear accelerator showed that IOR is a practical and safe procedure with demonstrable major tumoricidal effect in all five patients who came to autopsy. Although 13 of the 15 patients have died, none of the five autopsied patients succumbed to a local recurrence in the treated area. To avoid complications with IOR the radiation doses should be kept below 3000 rads for small volumes and below 2000 rads for large volumes. If these limits are respected and the intestines, except the involved duodenum, are kept out of the radiation beam, the risk and inconvenience of adding IOR to the usual abdominal exploration with biopsy and bypass is negligible. If, however, abdominal exploration and bypass have already been performed, a second operation for the purpose of IOR is advised only if the primary is small and no metastases are demonstrated.

133. FERMILAB CANCER THERAPY FACILITY

Cohen, L., Awschalom, M., Hendrickson, F., Rosenberg, I., Hrejsa, A., Kaul, R., Mansell, J., Zimmer, D., Bennett, B., Pientak, B., Universities Research Assn. Inc., *2100 Pennsylvania Ave. N.W., Washington, District of Columbia*, 20037, United States of America

The overall objective of the study is to continue a major research program for clinical trials in fast neutron therapy in order to evaluate the effectiveness of neutron therapy relative to other forms of conventional radiation therapy. Since all essential preclinical physical measurements and calibration, radiobiological studies, and pilot studies on patients referred with locally advanced disease have been completed satisfactorily, our objective at this stage is a strictly controlled experiment within a cooperative national protocol to evaluate one modality against another in randomly selected groups of patients. This work will concentrate mainly on subjects eligible for entry into the RTOG protocols: Resectable and Nonresectable Late Stage Cancer of the Head and Neck, Malignant Brain Tumors, Cancer of the Prostate and Bladder, Late Stage Carcinoma of the Cervix, Carcinoma of the Esophagus, Small Cell Carcinoma of the Lung, Carcinoma of the Pancreas, Tumors of Salivary Glands, Radioresistant Adenocarcinomas, Bone and Soft Tissue Sarcomas.

134. RADIATION THERAPY FOR UNRESECTABLE PANCREAS CARCINOMA

Livstone, E. M., Yale University, School of Medicine, Dept. of Medicine, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

135. PI-MESON RADIOTHERAPY OF ADENOCARCINOMA OF THE PANCREAS

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This is part of a broader project. A summary of this subproject is not available.

136. COMBINED INTERSTITIAL AND HIGH DOSE EXTERNAL BEAM THERAPY FOR PANCREAS CANCER

Dobelbower, R. R., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

3. COMBINED MODALITY AND OTHER THERAPEUTIC METHODS

137. PHASE II CONTROLLED RANDOMIZED CLINICAL TRIAL OF COMBINATION CHEMOTHERAPY IN PANCREATIC CARCINOMA, ROLE OF TUMOR MARKERS (ABBREV)

Williams, R., University of London, King's College Hospital Medical School, Liver Unit, *Denmark Hill, London SE5 8RX, England, United Kingdom*

OBJECTIVE AND APPROACH: (a) Histological Type and Clinical Stage of Cancer - All pancreatic carcinomas of non-endocrine origin will be included. All clinical stages I-IV will be included. (b) Treatment Modalities and Agents - (1) Induction: 5 FU 800 mg/m2 i/v; mitomycin C 10 mg/m2 i/v stat; adriamycin 20 mg/m2 i/v. (2) Maintenance: 5 FU 800 mg/m2; adriamycin 20 mg/m2 monthly i/v stat; mitomycin C 10 mg/m2. Followed at eight weeks after induction by a month's course of radiotherapy, giving 4000 rads at 200 rads per daily fraction. Half the patients entering the trial will be randomized as controls. (c) Protocol Outline - The patients will be evaluated using ultrasound, CXR, liver scan and, where necessary, ERCP.

Levels of tumor markers, notably pancreatic oncofoetal antigen, will be measured in serum and pancreatic juice when ERCP is performed. This will be followed by a staging laparotomy, at which a pancreatic biopsy will be taken. After randomization, progress will be monitored by clinical examination, ultrasound and sequential POA levels in the serum.

PRESENT STATUS: Total number of anticipated patients should be 100. Four have entered so far.

138. TREATMENT OF PANCREATIC CANCER

Kalser, M. H., Barkin, J. S., Lessner, H. H., Livingston, A., Morales, A., Troner, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1201 Northwest 16th St., Miami, Florida,* 33125, United States of America

Involved are three protocols for the treatment of pancreatic carcinoma depending on the extent of the disease. The first is adjuvant therapy following surgery, the second for locally unresectable lesions and the third for advanced disease. The first protocol randomizes into 2 areas: no therapy vs. combined radiation (4000R) and chemotherapy (5FU), the second has two areas; 6000R and 5FU or 4000R and adriamycin. The third protocol involves randomization to a combination of 1) 5FU, mitomycin-C and streptozotocin, 2) chlorozotocin, 3) maytansine, 4) galactitol, 5) 5FU, adriamycin & mitomycin. As of this date, 10 patients have been placed on the first protocol. No significant differences in survival or time of recurrence have been observed in the small sample available for analysis. Sixteen patients have been placed on the locally unresectable protocol. The results for this study are blind using the letters A and B. No tumor responses to therapy have been reported. Median time to document progression is 24 weeks for patients assigned to treatment A and 17 weeks for patients assigned to treatment B. When the study was designed, it was estimated that 72 evaluable patients would be required on each treatment arm to detect a 60% difference in survival time. Ninety-one patients have been randomized on the third protocol. This protocol previously involved ICRF-159 and B-2 deoxythioguanosine. These two arms were terminated since these drugs did not show any increase in quality of life in patients. There have been eleven tumor responses to therapy among patients receiving the five currently active arms as either the initial or crossover treatment. This protocol is an open-ended set of Phase II clinical trials designed to evaluate the anti-tumor activity of a number of drugs and drug combinations. The presently active treatment arms (FMS (5FU, mitomycin-C and streptozotocin), maytansine, chlorozotocin, galactitol and FAM (5FU, adriamycin and mitomycin)) are in too early a stage for any specific inferences to be summarized.

139. 125I, 5-FU, AND EXTERNAL RADIOTHERAPY FOR PANCREATIC CANCER

Dobelbower, R. R., Medical College of Ohio at Toledo, School of Medicine, Dept. of Radiology, *Box 6190, Toledo, Ohio,* 43614, United States of America

The overall objective of the proposed research is to improve survival and palliation for patients with locally unresectable adenocarcinoma of the pancreas.

Of all the patients diagnosed with adenocarcinoma of the pancreas, only about 10% are candidates for definitive surgery. Approximately half of the remaining patients are considered unresectable because of the local extent of disease rather than distant metastases. At present, almost all of these patients die of cancer. The proposed project addresses this group of patients with a combination of three treatment modalities that have previously shown promise in this disease: interstitial implantation of radioactive sources into the tumors, precision high dose (PHD) external beam radiotherapy, and 5-fluorouracil (5-FU) adjuvant chemotherapy. Forty-five patients with locally unresectable pancreatic carcinoma will be studied over the course of 3 years. Pre-treatment: The local and distant spread of disease will be studied extensively, as will the status of organs adjacent to the pancreas. Intraoperative interstitial implants of 125I will deliver local tumor doses of approximately 14,000 RAD. PHD external beam radiation therapy from an 18 MV linear accelerator will deliver 6000 RAD in 7 weeks to the tumor plus a margin of 1-2 cm. Subsequent adjuvant 5-FU will be given weekly intravenously in a dose of 500 mg/m2. Patients will be followed regularly and studied with regard to the local toxic effects of combined modality therapy. Local toxicity will be analyzed as a function of total combined radiation dose. Patient survival will be compared to that of patients treated by PHD therapy alone and to historical controls.

140. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

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Independently and not as an agent of the Government, The Contractor shall exert its best efforts to conduct studies and to carry out clinically indicated modes of therapy as these involve patients with pancreatic carcinoma. The therapeutic regimens, as well as the ensuing studies, will be performed on at least twenty-five patients per year, each of whom has a microscopically confirmed diagnosis of pancreatic carcinoma; and whose primary neoplasm has been staged and further characterized according to histological type. The studies will be conducted in accordance with the following protocols: Combined 5-Fluorouracil and Supervoltage Radiation Therapy as an Adjuvant to Surgical Treatment of Pancreatic Carcinoma; and a Controlled Evaluation of High Dose (6000R) Radiation Therapy, High Dose Radiation Therapy plus 5-FU, and Medium Dose (4000R) plus 5-FU in the Treatment of Locally Unresectable Carcinoma of the Pancreas.

141. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

Moertel, C. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct studies and to carry out clinically indicated modes of therapy as these involve patients with pancreatic carcinoma. The therapetic regimens, as well as the ensuing studies, will be performed on at least twenty-five (25) patients per year, each of whom has a microscopically confirmed diagnosis of pancreatic carcinoma, and whose primary neoplasm has been staged and further characterized according to histological type. The studies will be conducted in accordance with the following protocols: Combined 5-fluorouracil and supervoltage radiation therapy as an adjuvant to surgical treatment of pancreatic carcinoma; and a controlled evaluation of high dose (6000R) radiation therapy, high dose radiation plus 5-FU, and medium dose (4000R) plus 5-FU in the treatment of locally unresectable carcinoma of the pancreas.

142. THERAPY OF PATIENTS WITH PANCREATIC CARCINOMA

Spiro, H. M., Yale University, School of Medicine, Dept. of Internal Medicine, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This project proposes to improve the palliation and survival of patients with pancreatic carcinoma by randomized, controlled, stratified treatment programs involving chemotherapy and radiation therapy. The objectives and scope of the renewal period have not changed significantly from the prior reporting period.

143. PHASE II STUDIES IN GASTROINTESTINAL CANCER

Moertel, C. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

Studies will be performed on a minimum of forty patients per year with either pancreatic or gastric cancer and an additional forty patients with colorectal cancer. Contractor facilities will be adequate for approximately ten inpatients, space for outpatient visits, laboratories, and offices. Patients treated will be provided bed, nursing and laboratory services, drugs, and supplies consistent with a good clinical research unit. Participation and interest by surgery, radiology, clinical pathology, and medical departments is necessary for performance of these Phase II studies. In addition, the Contractor will have adequate knowledge of nutritional derangements related to GI cancer and its treatment and must have capabilities to provide hyperalimentation or other supportive care measures to control nutritional imbalances.

144. IMMUNE STUDIES IN MALIGNANT DISEASE

Sindelar, W. F., Kurman, C., Dresdale, A., Tepper, J., Travis, E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Surgery Branch, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Patients with sarcomas are studied for evidence of serum reactivity against tumor-specific determinants expressed on cultured syngeneic and allogeneic tumor cells using techniques of immunofluorescent staining. Roles of tissue-specific xenogeneic antibodies are investigated for possible approaches to developing methods of immunotherapy in a carcinogen-induced pancreatic carcinoma in hamsters. Intraoperative radiotherapy in dogs is evaluated for dose-response and normal tissue tolerance to electron-beam irradiation as part of an attempt to adapt operative radiotherapy to the treatment of human abdominal malignancies.

BIBLIOGRAPHIC REFERENCES: Hadley, N.A., and Sindelar, W.F.: Antifetal and tumor-specific reactivity in human osteosarcoma. Surg. Forum 30: 122-124, 1979. Rosenberg, S.A., Tondreau, S.C., Shoffer, P.C., Hyatt, C., Brown, J.M., Thorpe, W., and Sindelar, W.: Serologic analysis of human tumor antigens. II. Reactivity of sera from eleven osteogenic sarcoma patients against autologous and allogeneic tumor cells. Surgery 86: 258-265, 1979.

145. ADMINISTRATION OF NATIONAL PANCREATIC CANCER PROJECT

Cohn, I., Liebow, C., Louisiana State University, Medical Center, School of Medicine, Dept. of Surgery, *1542 Tulane Ave., New Orleans, Louisiana,* 70112, United States of America

The National Pancreatic Cancer Project is a grant-supported Organ Site Program of the National Cancer Institute. Its purpose is to plan, support, stimulate and monitor pancreatic cancer research through the use of grants mechanism. The Project also acts as an information center for investigators involved or interested in pancreatic cancer research and for clinicians treating patients with pancreatic cancer.

BIBLIOGRAPHIC REFERENCES: Beazley, R.M., and Cohn, I., Jr.: Pancreas. Chapter in: Surgical Oncology. E.M. Copeland, III, Editor. John Wiley and Sons, Inc. In press, 1980. Cohn, I., Jr.: The Meaning of Lymph Nodes and Their Effective Treatment as Related to Stomach, Pancreas, and Small Bowel. Chapter in: Lymphatic System Metastasis. G.K. Hall and Co. In press, 1980.

146. COMBINED MODALITY THERAPY FOR CARCINOMA OF THE PANCREAS (HUMAN)

Wiley, A. L., University of Wisconsin, Madison Campus, Center for the Health Sciences, Dept. of Radiology, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

V. OTHER STUDIES OF ENDOCRINE OR HORMONE-PRODUCING NON-ENDOCRINE TUMORS

147. HUMAN CANCER - ORIGIN AND GENETIC MARKERS

Fialkow, P. J., Friedman, J. M., Penfold, G., University of Washington, School of Medicine, Dept of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

The general objective is to utilize genetic markers to investigate the cause and pathogenesis of human tumors. The primary approach involves determining the number of cells from which tumors arise, thereby providing important clues to their mode of origin. For example, a neoplasm that results from a rare event, like 'spontaneous' somatic mutation, would be expected to arise in a single cell. This problem is investigated in subjects with at least two genetically distinct types of cells. Tumors with clonal origin contain only one cell type, whereas both types would be more likely in neoplasms arising in several cells. X-chromosome inactivation mosaicism in females heterozygous for the glucose-6-phosphate dehydrogenase (G-6-PD) locus is used to provide data relevant to the following questions which have important therapeutic implications: 1. Do the myeloproliferative disorders and leukemias have single or multiple cell origin? 2. Do they originate in pluripotent stem cells or more differentiated progenitors? 3. Are there residual normal stem cells in patients with hematopoietic neoplasms? 4. Do tumors which occur in syndromes clearly inherited by mendelian mechanisms have multicellular origin? 5. Do neoplasms with strong environmental influences (e.g., viral and endocrine tumors) have multicellular origin? 6. Does the pathogenesis of embryonal tumors and other cancers involve sequential mutations?

BIBLIOGRAPHIC REFERENCES: Fialkow, P.J.: Clonal and Stem Cell Origin of Blood Cell Neoplasms in Contemporary Hematology/Oncology. LoBue, Gordon and Silber, Eds. Plenum Publishing Corporation, New York. Vol. 1, 1980. pp. 1-46. Fialkow, P.J.: Studies with G6PD on the Origin of Human Neoplasms in Viruses in Naturally Occurring Cancer. Essex, M., Todaro, G., and Zur Hausen, H., Eds. Cold Spring Harbor Laboratory, Cold Spring Harbor. Vol. 7, 1980.

148. DELTA-5-3-KETOSTEROID ISOMERASE

Pollack, R. M., University of Maryland, Baltimore County Campus, Graduate School, Dept. of Chemistry, *Catonsville, Maryland,* 21228, United States of America

We wish to continue our investigation into the mechanism of action of delta-5-3-ketosteroid isomerase. This enzyme is a key enzyme in the biosynthesis of steroids, and a knowledge of its mechanism should allow selective modification by inhibitors, and consequently regulation of steroid biosynthesis. We hope to be able to use our knowledge of the mechanism of delta-5-3-ketosteroid isomerase to synthesize specific irreversible inhibitors of this enzyme which may be therapeutically useful in treating certain hormone-dependent cancers.

Our initial work has shown that beta-spiro-3-oxiranyl-5-androstan-17 beta-ol is an excellent active site-directed irreversible inhibitor of this enzyme. We wish to use this compound and its 17-acetate (also an excellent inhibitor) to probe the mechanism of the enzyme by radioactively labelling the active site. In addition, pH-rate profiles with these inhibitors should give information about active-site enzymes pKa's not previously obtainable.

These compounds and other suitable derivatives will also be submitted to the National Cancer Institute for testing for anti-cancer activity.

149. CANCER CLINICAL RESEARCH

Hickey, R. C., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *c/o Texas Medical Ctr., 6723 Bertner Ave., Houston, Texas,* 77030, United States of America

This Clinical Research Center Grant has been prepared to serve as the major source of support for the Clinical Research Center which consists of a 22 bed research unit and a 20 bed laminar air flow unit. Major divisions of clinical research which will be emphasized include the diagnosis of biology of clinical cancer and the therapy of human cancer. Included are protocols to evaluate cellular kinetics of tumor cells, diagnosis and management of hormone-producing tumors, early detection of tumor recurrence by polyamine analysis, evaluation of new drugs and drug regimens in malignant diseases, the use of laminar air flow rooms and prophylactic antibiotics in the chemotherapy of leukemia and breast cancer, development of new techniques for study of the immunology of cancer and its immunotherapy, and exploration of the pharmacology of antitumor drugs. Through intradisciplinary research in a specialized setting, it is anticipated that further progress will be made in the management of the cancer patient.

150. HORMONE PRODUCING NON-ENDOCRINE TUMORS (HUMAN)

Samaan, N. A., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Surgery, *c/o Texas Medical Ctr., 6723 Bertner Ave., Houston, Texas,* 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

151. USE OF SOMATOSTATIN ON DIARRHEA DUE TO ENDOCRINE ADENOMA OR SHORT BOWEL SYNDROME

Dobbins, J. W., Yale University, School of Medicine, Dept. of Internal Medicine, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

152. ENDOCRINE AND RADIOIODINATION CORE

Yen, S., University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California,* 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

INVESTIGATOR INDEX

Aamodt, R. 39
Abe, K. 107
Abele, R. 123
Adams, R.A. 110
Aires Correia, R. 86
Alberto, P. 123
Allan, B.J. 95
Anderson, T. 121
Angeles, A. 16
Aoki, T. 5
Arimura, G.K. 127
Ashayeri, E. 132
Atuk, N.O. 66
Awschalom, M. 133
Bagshawe, K.D. 74
Bale, W.F. 36, 82
Ban, J. 5
Barkin, J.S. 138
Bartrum, R.J. 131
Baylin, S.B. 56, 57
Becker, K.L. 33, 45
Benedetto, W.J. 36, 82
Benfield, J.R. 108
Bennett, B. 133
Berk, R.N. 111
Bodanszky, M. 73
Borgstrom, A. 68
Brennan, M. 39
Brodrick, J.W. 79, 92
Buchan, A.M. 72
Burrow, G. 22
Byrne, P. 121
Camargo, C.A. 10
Carbone, P.P. 124
Cerletty, J.M. 29
Chang Wai Ling, B.K. 125
Charles, M.A. 35
Charles, P. 20
Chaudhuri, T.K. 50
Chin, W.W. 104
Chisholm, R. 132
Chu, E.W. 39
Chu, M.Y. 119
Chu, T.M. 76
Clinton, B. 22
Cohen, L. 133
Cohn, I. 145
Cooper, D.S. 104
Cornwell, E.E. 132
Cox, C.E. 55
Cranston, J.W. 97
Danes, B.S. 101
Davis, M.A. 88
de los Angeles Contreras, M. 36
de los Angeles Contreras, M. 82
De Paula, P. 86
de Vet, B. 99
Deftos, L.J. 46
DeLand, F.H. 78
DeLellis, R.A. 47
DelMar, E.G. 92
DiMagno, E.P. 103
Dobbins, J.W. 151
Dobelbower, R.R. 136, 139
Dobyns, B.M. 48
Doppman, J.R. 1
Douglass, H.O. 69, 71, 76
Douple, E.B. 131
Dresdale, A. 144
Duke, D.I. 118
Dunnick, N.R. 63, 85
Elbrond, O. 20
Emmertsen, K. 20
Ensinck, J.W. 129
Erjavec, M. 41
Ezrin, C. 15
Fang, V.S. 3
Fein, H. 39
Fernandez Feijo, S.G. 86
Fialkow, P.J. 147
Field, J.B. 113
Fradkin, J. 39
Franklin, J. 94
Friedman, J.M. 147
Frohman, L. 60
Fujiwara, K. 84
Genel, M. 22
Genell, S. 68
Geokas, M.C. 79, 92
Gertner, J.M. 22
Givens, J.R. 11
Glitz, D.G. 96
Gold, D.V. 81
Goldrosen, M.H. 69, 70, 71
Goldson, A.L. 132
Goodale, R.L. 83
Goode, R.L. 42
Goodwin, D. 42
Gould, V.E. 37
Grady, E.D. 36, 82
Grant, A.G. 98
Greer, M.A. 13
Grover, M.R. 6
Guderley, H. 93
Gunther, G.R. 109
Hagen, T.C. 17
Halliday, W.J. 31
Hansen, H.H. 20
Hanson, R.N. 88
Harper, A.A. 126
Heisler, S. 93
Hellmann, K. 118
Hemmingsson, A. 87
Hendrickson, F. 133
HermonTaylor, J. 98
Hickey, R.C. 149
Hill, B.T. 4
Hoek, F. 99
Hofstadter, F. 51
Hoitsma, H.F. 99
Holyoke, E.D. 70
Homburger, F. 110
Honda, T. 91
Hood, A.J. 126
Horton, E.S. 116
Howell, J.H. 71
Hrejsa, A. 133
Huibregtse, K. 99
Hutchinson, G.E. 118
Irvin, G.L. 38
Jackson, C.E. 26
Johannessen, J.V. 37
Jones, A.E. 39
Kahn, C.R. 7
Kaiser, M.H. 138, 140
Kambouris, A.A. 26
Kaplan, S.A. 44
Kasina, S. 64
Kasugai, T. 84
Kaul, R. 133
Kendall, J.W. 2
Kieffer, J.D. 104
Kirsch, W.M. 8
Klavins, J.V. 80
Klibanski, A.C. 104
Kligerman, M.M. 135
Kmet, A. 41
Kolts, B.E. 105
Kovacs, K. 15
Kuno, N. 84
Kupchik, H.Z. 75
Kurimoto, K. 84
Kurman, C. 144
Ladurner, D. 51
Landsberg, L. 22
Largman, C. 79, 92
Laughlin, J.S. 90, 112
Lee, C.L. 76
Leitner, G. 51
Lessner, H.H. 138
Lieberman, L.M. 65
Liebow, C. 145
Line, B. 39
Livingston, A. 138
Livstone, E.M. 128, 134
Loewenstein, M.S. 75
Loor, R. 76
Maloof, F. 104
Mansell, J. 133
Marino, C.A. 64
Marks, W. 68
Matsumura, K. 108
Matsuura, A. 84
Matthews, M. 121
McCrossan, M.V. 72
Melvin, J. 119
Milgrom, F. 77
Moertel, C.G. 141, 143
Moore, M.C. 70
Moossa, A.R. 89
Morales, A. 138
Morton, M. 35
Mosekilde, L. 20
Murad, F. 114
Mushens, J. 126
Mutt, V. 73
Nayfield, S.G. 120
Nicoloff, J.T. 40, 43
Nielsen, H.E. 20
Nunes, J.E. 49
O'Dorisio, T.M. 117
Oguri, T. 84
Ohlsson, K. 68
Oka, Y. 107
Page, S. 22
Paladugu, R.R. 108
Paloyan, E. 58, 59
Passaro, E.P. 100

Pearse, A.G. 72
Penfold, G. 147
Peres, O. 49
Perzin, K.H. 37
Pessoa, J.B. 86
Pientak, B. 133
Pinsky, S. 60
Polak, J.M. 72
Polcyn, R.E. 65
Pollack, R.M. 148
Porter, J.M. 6
Pretorius, H.T. 39
Price, L.A. 4
Pym, B. 118
Ramirez Mendoza, P. 16
Rau, P. 75
Rayford, L.L. 132
Reichlin, S. 61, 62
Riddle, M.C. 130
Ridgway, E.C. 104
Rinderknecht, H. 106
Robbins, J. 39
Roberts, D.W. 131
Robinson, A.G. 14
Rosenberg, I. 133
Roth, J. 7
Roux, V.J. 132
Rubenstein, A.H. 115
Rubin, P. 12
Rusted, I.E. 34
Said, S.I. 73
Samaan, N.A. 150
Sanani, S. 122
Saunders, R.L. 131
Scheele, G.A. 94
Schein, P.S. 121
Schmillevitch, J. 49
Schneider, A. 39
Schneider, A.B. 60
Schultz, D.R. 127
Seematter, R. 123
Senciall, I.R. 34
Serson, D. 49
Service, F.J. 102
Sharma, B. 35
Shawker, T. 63
Shimano, T. 76
Shimaoka, K. 25
Silva, O.L. 33, 45
Sindelar, W.F. 144
Singer, F.R. 28
Sisson, J.C. 27
Sizemore, G.W. 24
Smith, F.P. 121
Smy, J.R. 126
Snajder, J. 41
Soares, W.E. 49
Sobrinho Simoes, M.A. 37
Soklic, M. 41
Spaulding, M.B. 122
Spiro, H.M. 142
Spitznagle, L.A. 64
Strohbehn, J.W. 131
Strott, C. 7
Strott, C.A. 1
Suttle, D.P. 5
Talerman, A. 32
Tangen, K. 37
Tashjian, A.H. 26
Tegner, H. 68
TeleniusBerg, M. 19
Tepper, J. 144
Teunen, A. 99
Thomas, C.G. 52
Thorner, M.O. 18
Travis, E. 144
Troner, M. 138
Tytgat, G.N. 99
Ultmann, J.E. 53
Valenta, L.J. 35
van der Pompe, W.B. 32
Veitch, R.K. 126
Wallace, H.J. 25
Walsh, J.E. 131
Weber, G. 5
Weickmann, J. 96
Weintraub, B.D. 39
Wells, S.A. 21, 30, 54
Westfall, T.C. 66
White, T.T. 95
Widerlite, L. 121
Wiley, A.L. 146
Williams, G.A. 23
Williams, R. 137
Wolfe, H.J. 47
Woolley, P.V. 121
Wu, M. 127
Yamaguchi, K. 107
Yen, S. 152
Yen, S.S. 9
Yunis, A.A. 127
Zamcheck, N. 75
Zimmer, D. 133
Zamoff, B. 67

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